Demystifying Medicine: Inflammatory Bowel Disease

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Outline

- Patient Presentation
- Definition
  - Epidemiology
  - Etiology
- Clinical Presentation
- Treatment Options

Definition

- **Idiopathic chronic inflammation** of GI tract
  - Ulcerative colitis
    - Limited to mucosal layer of colon
  - Crohn's disease
    - Full thickness inflammation involving any part of the GI tract (mouth to anus)
- NOT IBS!!!! (irritable bowel syndrome)
- Etiology?
  - Hyperactive mucosal immune response to environment

IBD: Overview

- Scope of the disorder (United States)[1]
  - 700,000 physician visits per year
  - 100,000 hospitalizations per year
  - Crohn's disease accounts for two thirds
- Long-term outlook
  - Chronic, lifelong disease
  - Surgery for 50% to 80% of CD patients
  - Surgery for 30% of UC patients
  - Acute flare-ups alternating with remission
  - Complications from therapy and disease

1. Calkins BM. *Digestive Diseases in the United States: Epidemiology and Impact*. Bethesda, Md: NIH; May 1994:511.

Notable People

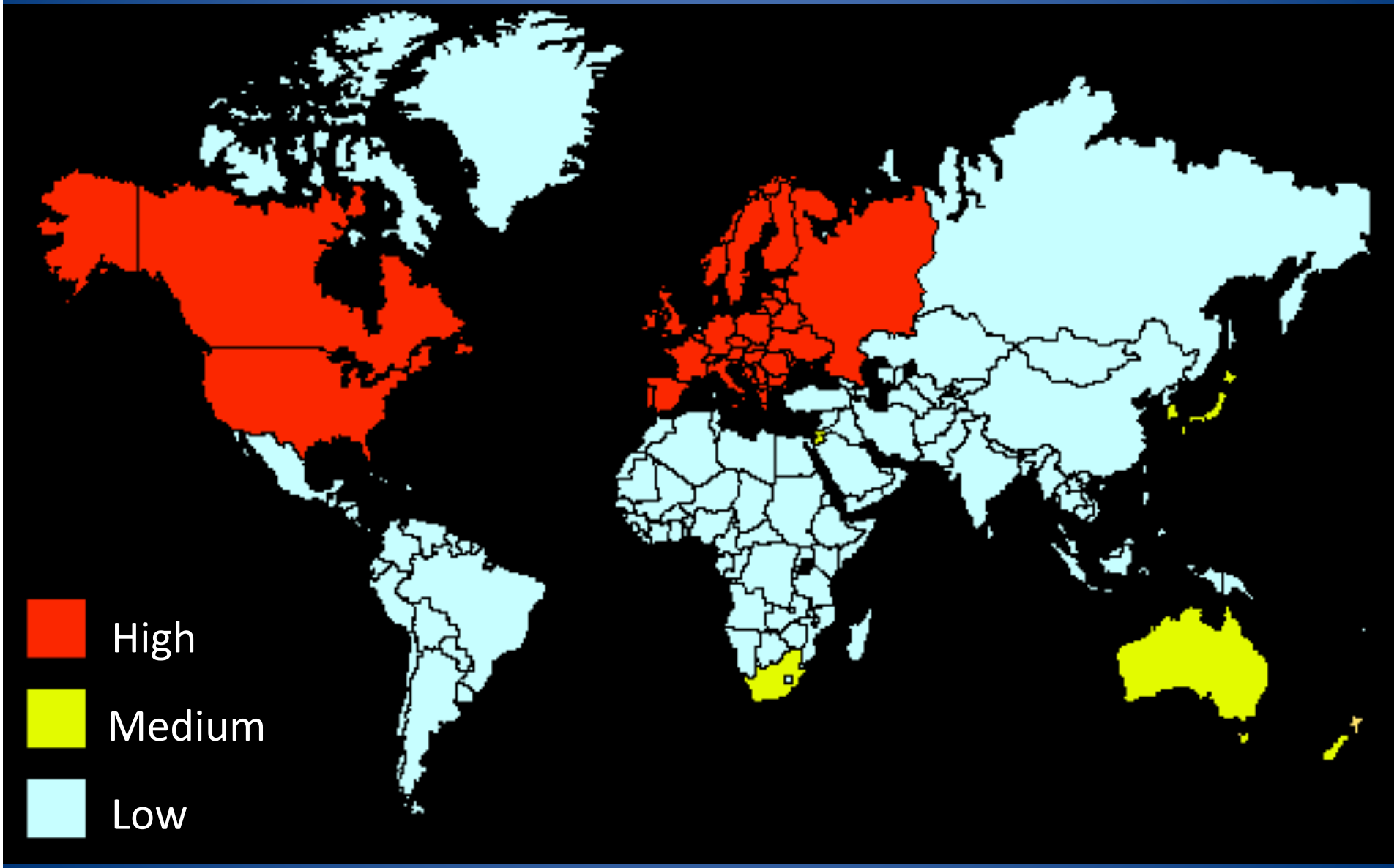
- Crohn's Disease
  - Dwight D. Eisenhower – 34th President
  - Shannon Doherty – Actress
  - David Garrard – NFL Quarterback
- Ulcerative Colitis
  - Tony Snow – former WH Press Secretary
  - Marvin Bush – son of George W. Bush

IBD in the United States

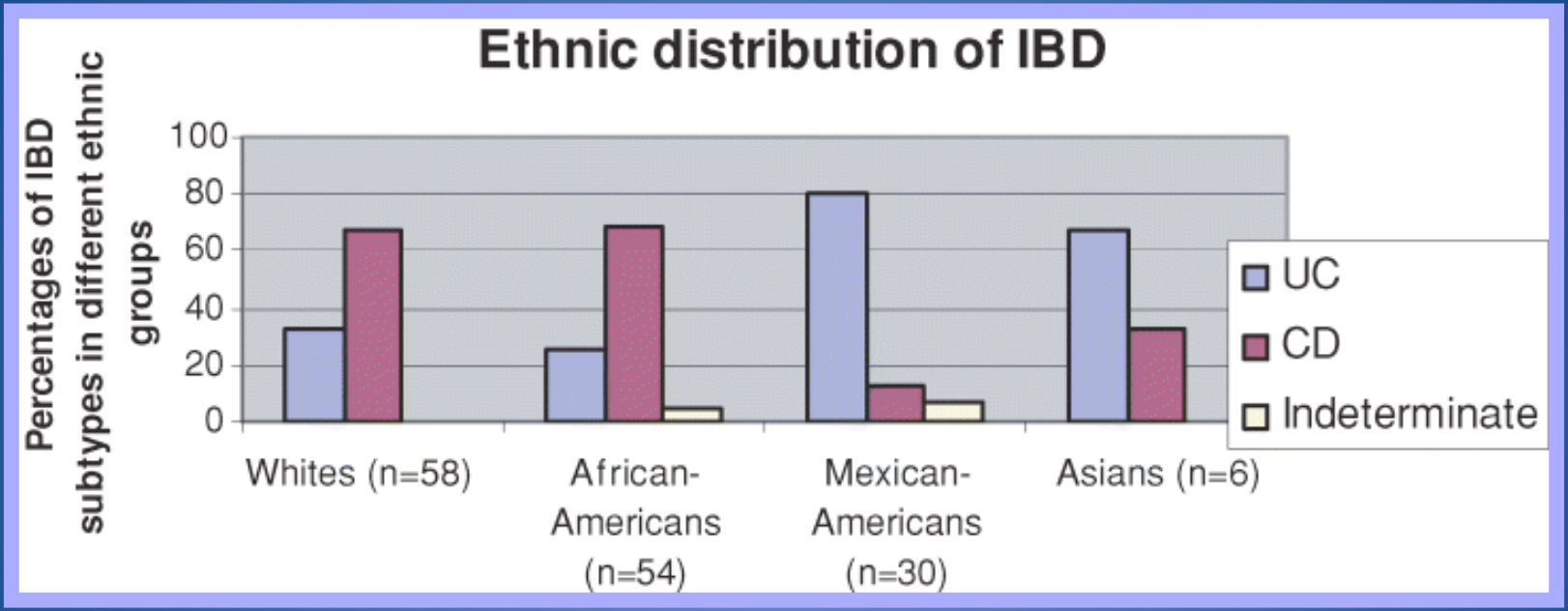
- Incidence: 10 cases per 100,000 per year
  - Onset: 30% between 10 and 19 years[3]
  - Young children: 2%[3]
- Prevalence: 100 cases per 100,000[1]
  - More than 1 million cases estimated in United States
  - Ulcerative colitis: 50%[2]
  - Crohn's disease: 50%[2]

1. Hanauer SB. *Cecil Textbook of Medicine*. 20th ed. Philadelphia, Pa: WB Saunders Co; 1996:707.
2. Calkins BM. *Digestive Diseases in the United States: Epidemiology and Impact*. Bethesda, Md: NIH; May 1994:511.
3. Grand RJ et al. *Clin Invest Med*. 1996;19:373.

Global Prevalence of IBD



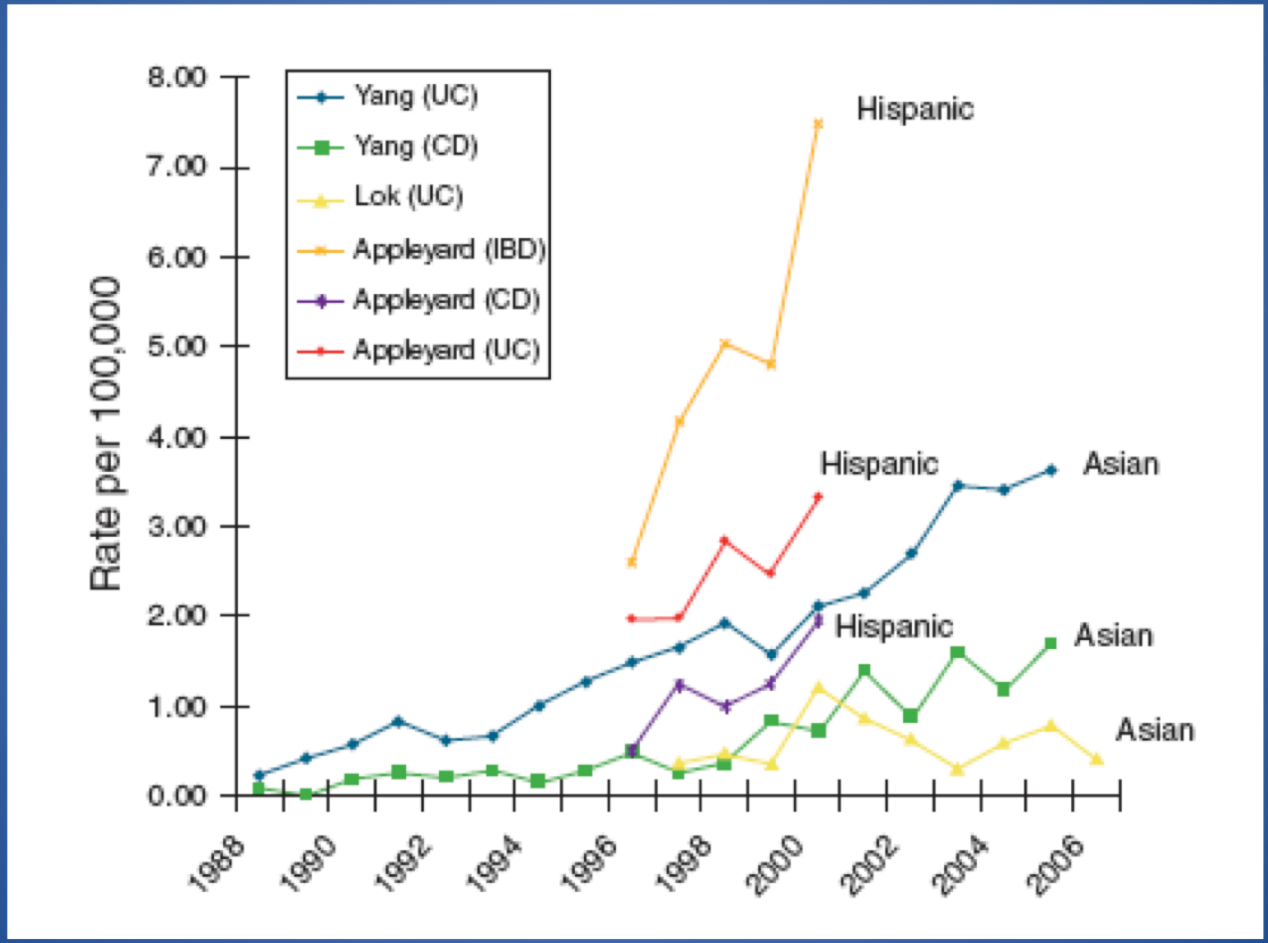
Impact of Race and Ethnicity



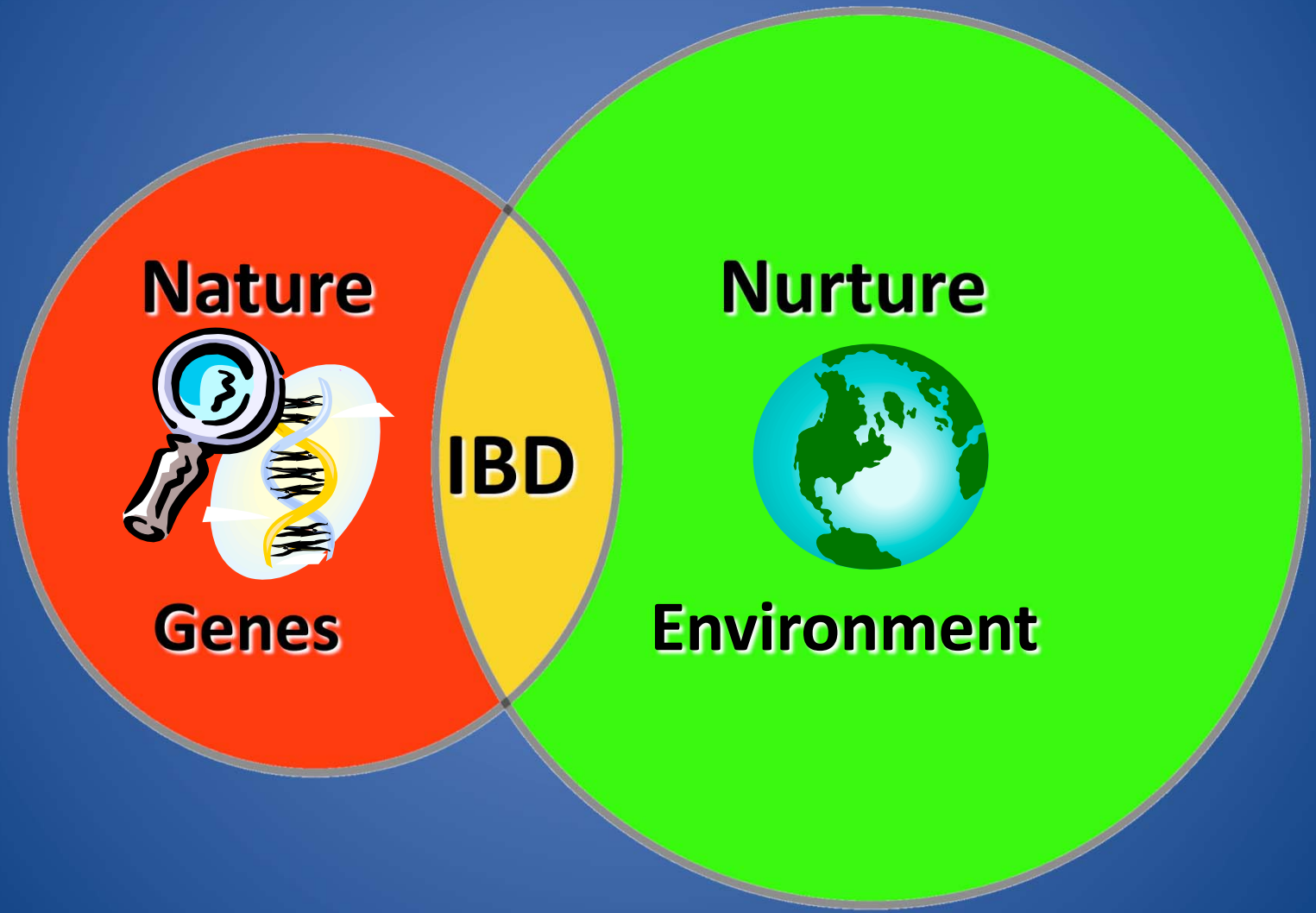
- **Whites had stronger family history of IBD and colorectal cancer.**
- **African Americans with CD had higher incidence of arthritis.**
- **Disease severity similar across all groups.**
- **P-anca served as a sensitive maker for Mexican Americans as 100% with UC were positive compared with 40% in whites**

Basu, D; Am J Gastroenterology 100:2254-2261, 2005

Rising Incidence in Hispanics, Asians



Etiologic Interplay



Genetic Susceptibility

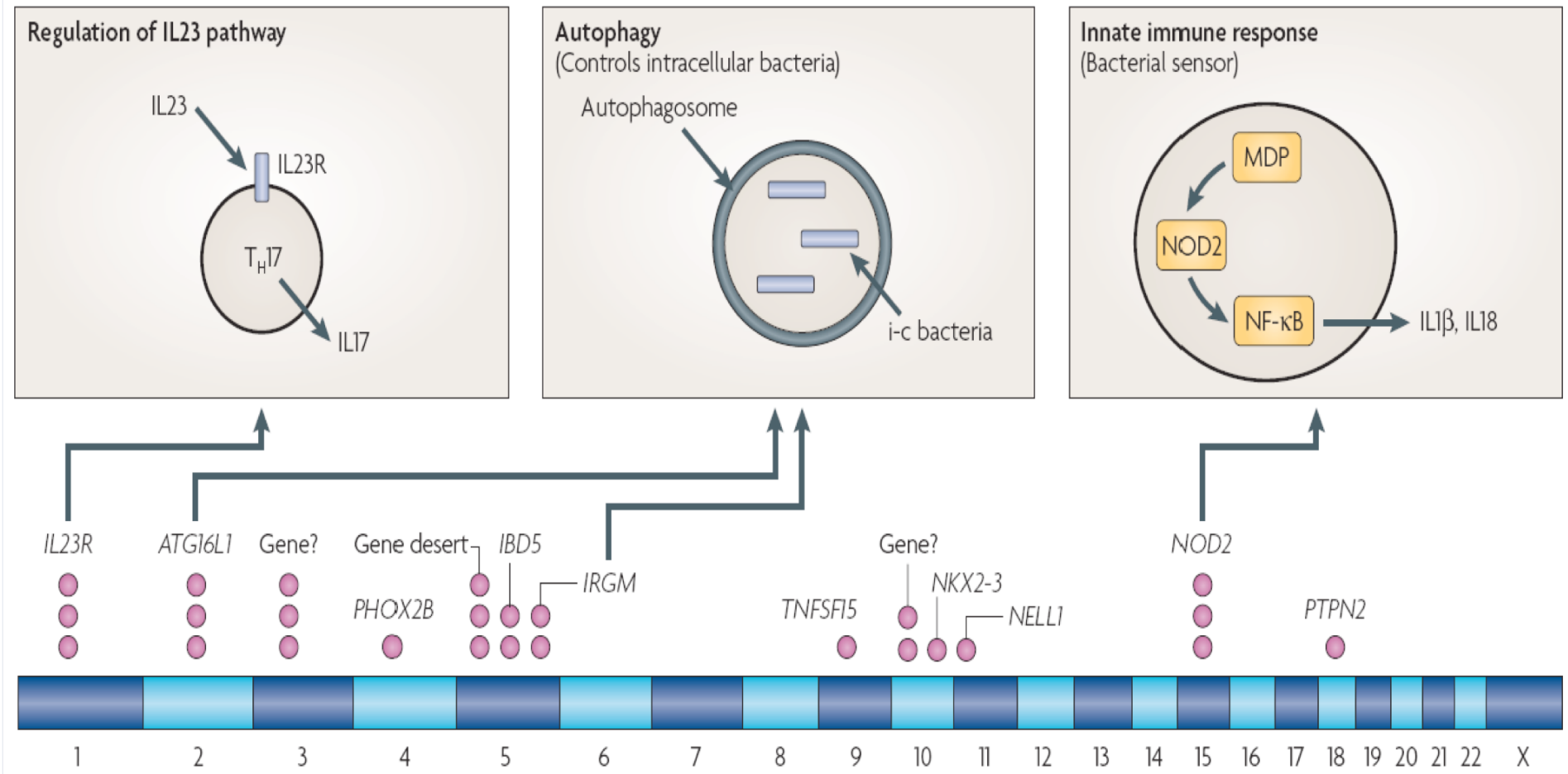
Concordance in twins:

Shows the importance of environmental inputs

	CD	UC
Monozygotic	44-50%	5-14%
Dizygotic	8%	0%

Tysk et al. Gut 1988; 29:990
Ornholm M et al. Scand J. Gastroenterology 2000; 35:1075

Genetic Polymorphisms



Mathew CG. Nat Rev Gen 2007; 9:9-14

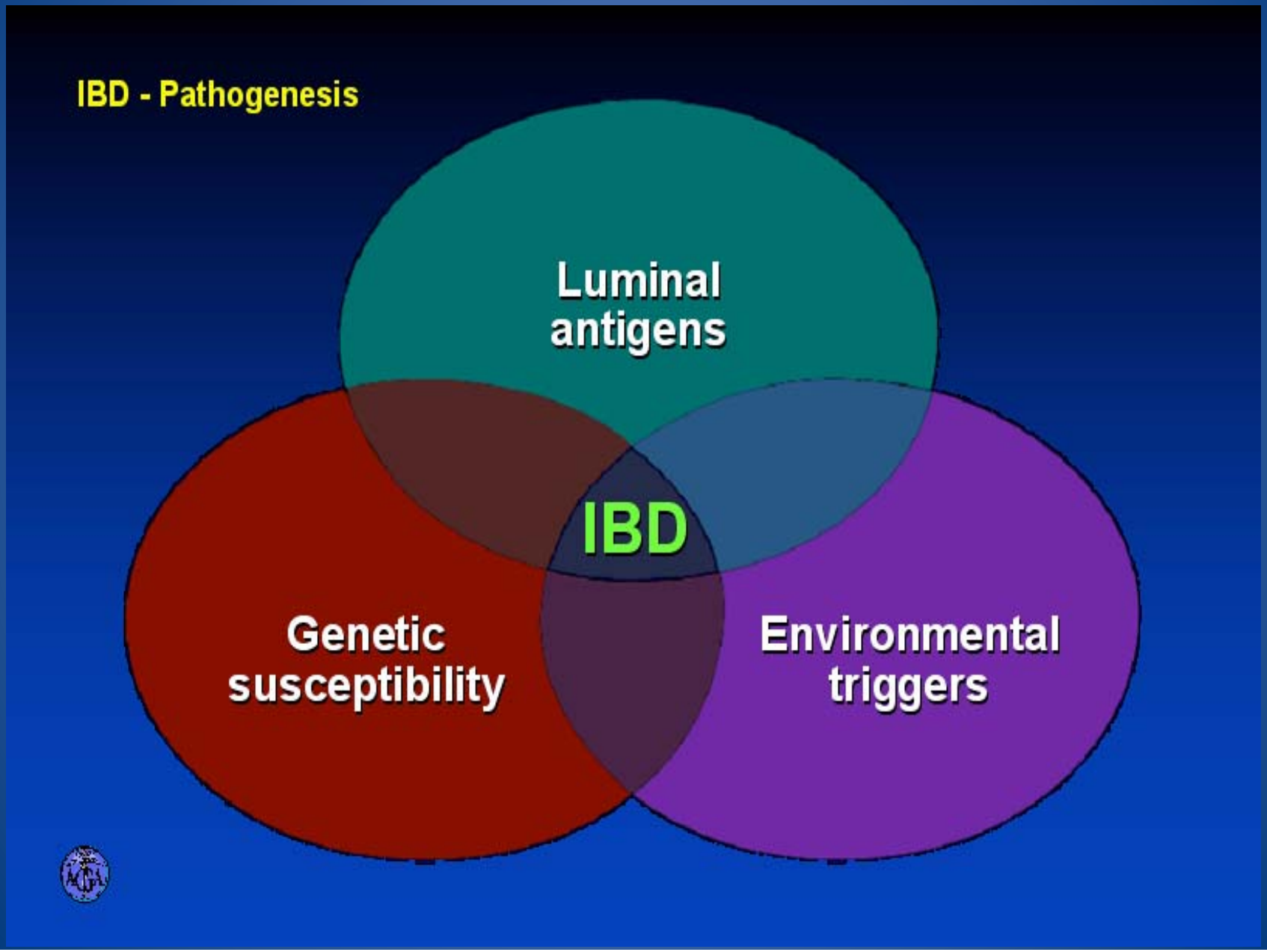
Table 2 | **Gene associations in Crohn's disease and ulcerative colitis**

Chromosome	Location (Mb)	Genes of interest	Associated with Crohn's disease	Associated with ulcerative colitis
1p31	67	*IL23R*	Yes	Yes
2q37	231	*ATG16L1*	Yes	No
3p21	49	Multiple, including *MST1*	Yes	Yes
5p13	40	Intergenic, *PTGER4*	Yes	No
5q31	131	Multiple, including *SLC22A5*	Yes	Unclear
5q33	150	Multiple, including *IRGM*	Yes	No
5q33	158	*IL12B* (p40)	Yes	Yes
10q21	64	ZNF365	Yes	Unclear
10q24	101	*NKX2-3*	Yes	Yes
16q12	49	*NOD2*	Yes	No
17q21	37	Multiple, including *STAT3*	Yes	Yes
18p11	12	*PTPN2*	Yes	Unclear

ATG16L1, autophagy related 16-like protein 1; *IL12B*, interleukin-12β; *IL23R*, interleukin-23 receptor; *IRGM*, immunity-related GTPase family, M; *NKX2-3*, NK2 transcription factor related, locus 3; *NOD2*, nucleotide-binding oligomerization domain protein 2; *PTGER4*, prostaglandin receptor, EP4; *PTPN2*, protein tyrosine phosphatase, non-receptor type 2; *SLC22A5*, solute carrier family 22, member 5; *STAT3*, signal transducer and activator of transcription 3; *ZNF365*, zinc-finger protein 365.

Cho JH. Nat Rev Immun 2008; 8:458-66

Gene-Environment Interaction



Etiology

- Genetics
  - More common – N. Europe, Jewish (Ashkenazi)
  - Multiple associated genes
    - CARD15/NOD2
  - 10-15% IBD pts have relative with IBD
- Environment?
  - Industrialized nations, colder climates
  - Bacteria important
  - Tobacco use
    - Ulcerative colitis – Non-smokers
    - Crohn's disease – Smokers

Environmental Factors and IBD

- SMOKING

- CLIMATE
  - IBD more common in cold climates

- INDUSTRIALIZED NATIONS
  - IBD more common in industrialized nations

- INFECTIONS

- ANTIBIOTICS

- NSAIDS
- DIET?

- STRESS?

Etiologic Hypotheses

Persistent infection

- Mycobacteria
- *Helicobacter* sp.
- Measles-mumps
- Listeria
- Toxigenic *E. coli*

Defective mucosal integrity

- Altered mucus
- Increased permeability
- Cellular starvation
- Impaired restitution

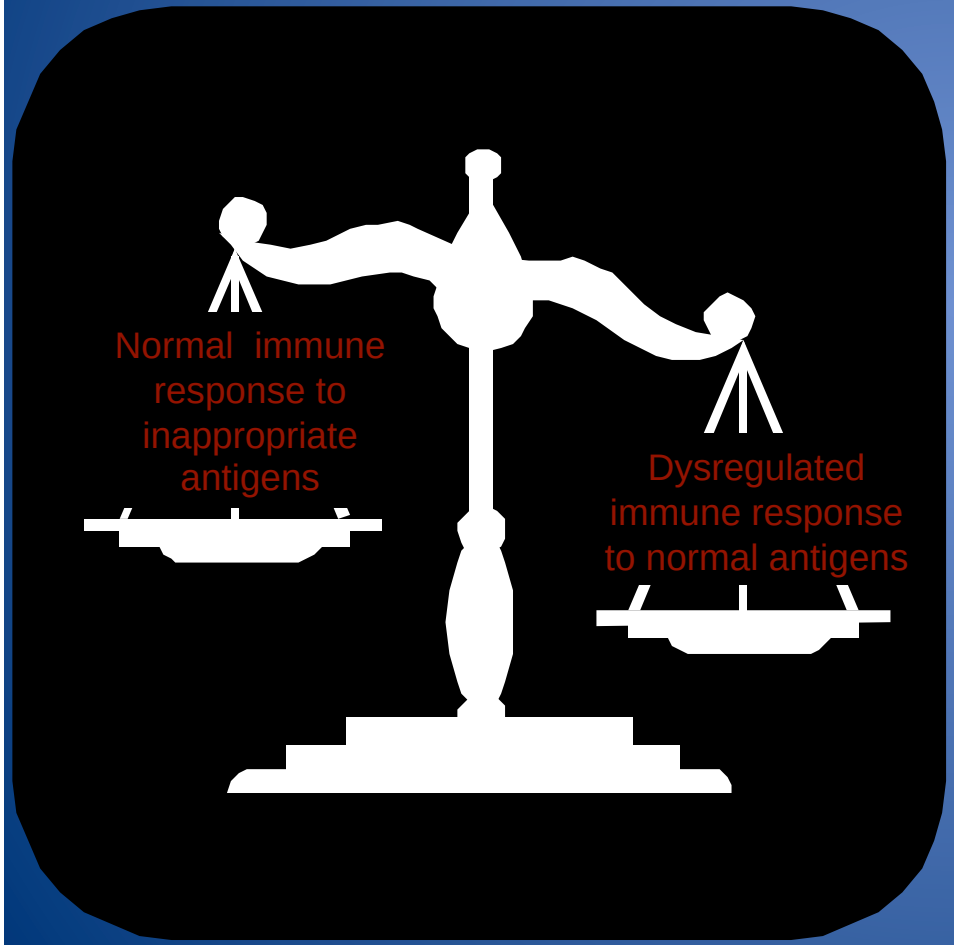
Dysbiosis

- ↓ protective bacteria
- ↑ aggressive commensals

Dysregulated immune response

- Loss of tolerance
- Aggressive cellular activation
- Defective apoptosis

The chronic inflammation of IBD is due to a dysregulated immune response to antigens in the intestine



- Innate and adaptive immune system
- Epithelial barrier function
- Composition of microbial flora
- Genetic and environmental exposures
- Defects in regulatory mechanisms

Outline

- Patient Presentation
- Definition
- Clinical Presentation
  - Clinical Features
  - Diagnosis
    - Radiology
    - IBD Antibodies
- Treatment Options

Clinical Features

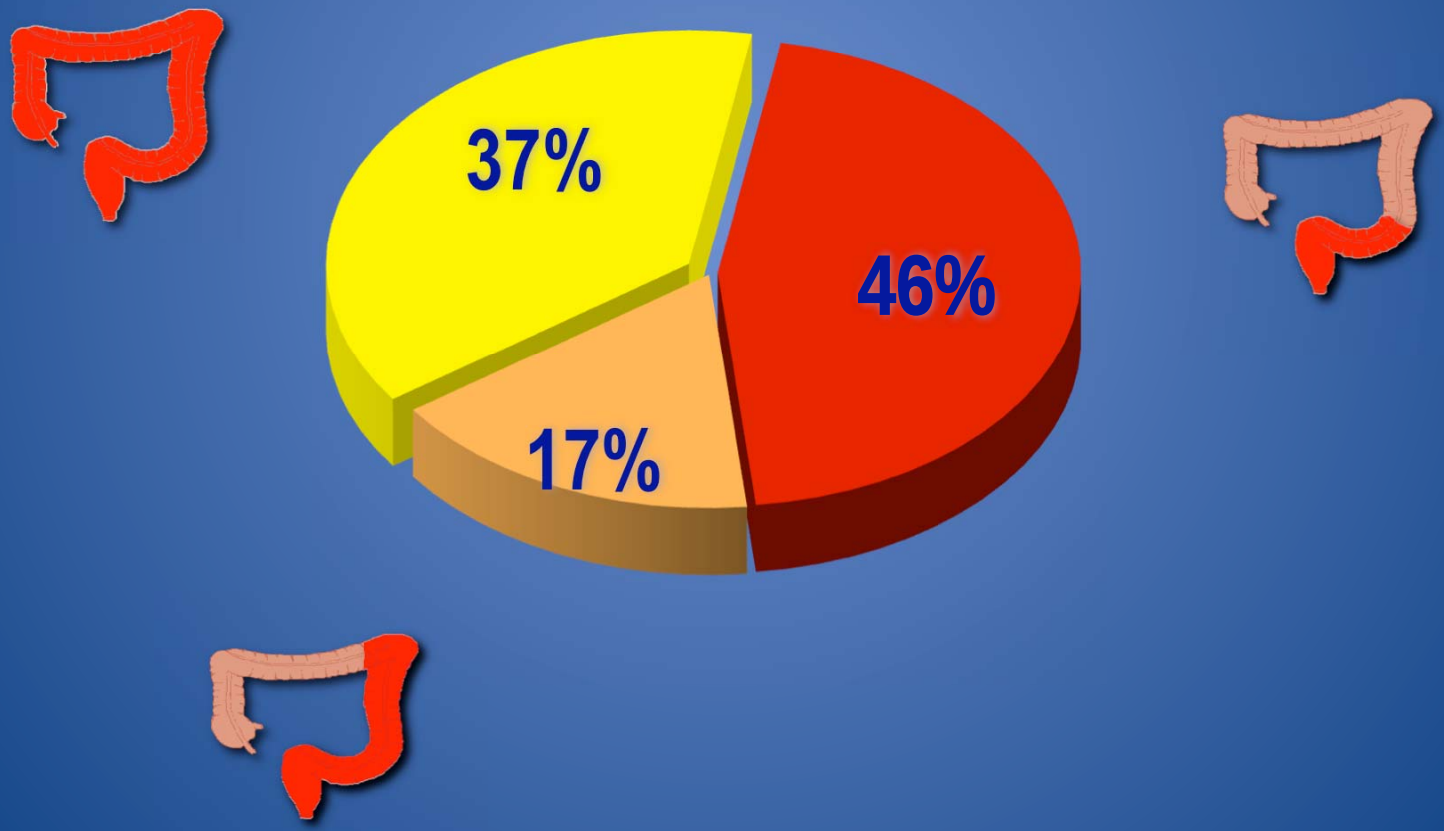
Clinical Feature	Ulcerative Colitis	Crohn's
Inflammation	Superficial, continuous	Full thickness, patchy
Mucosal Ulcers	Superficial	Deep, linear
Involvement	Rectum, colon	Ileum, colon
Extra-intestinal	Yes	Yes
Fistulas	No	Yes
Symptoms	Bloody diarrhea, urgency	Diarrhea, pain, weight loss

Presentation of UC

- Symptoms depend on extent and severity of inflammation
- Bloody diarrhea
- Abdominal cramping
- Tenesmus- fecal urgency
- Constipation when disease is only distal
- Systemic symptoms, fever, decreased stamina, weight loss
- Extraintestinal manifestations (1/3 patients)

Disease Distribution at Presentation: UC

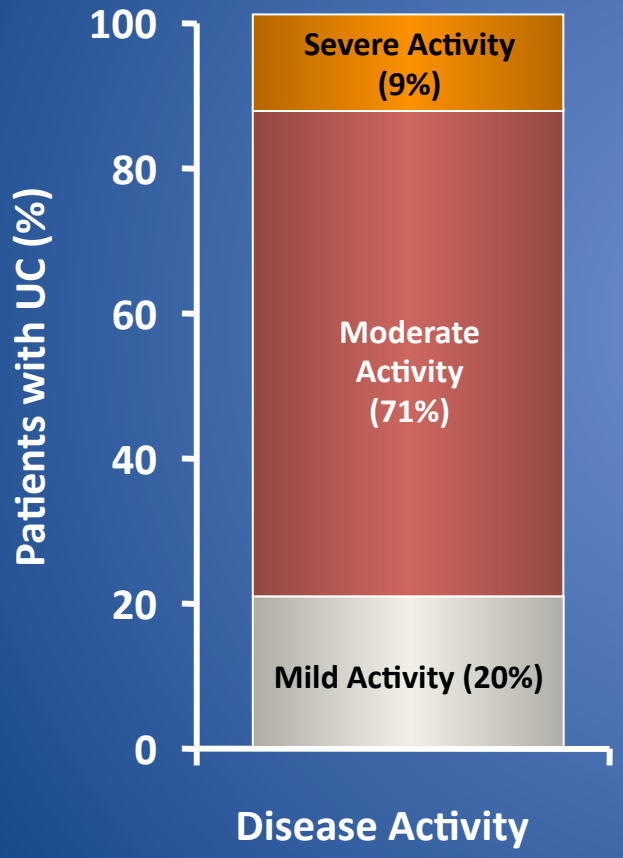
n = 1116



Farmer RG, Easley KA, Ranking GB. *Dig Dis Sci* 1993;38(6):1137-1146

UC: Natural History

Disease Severity at Presentation

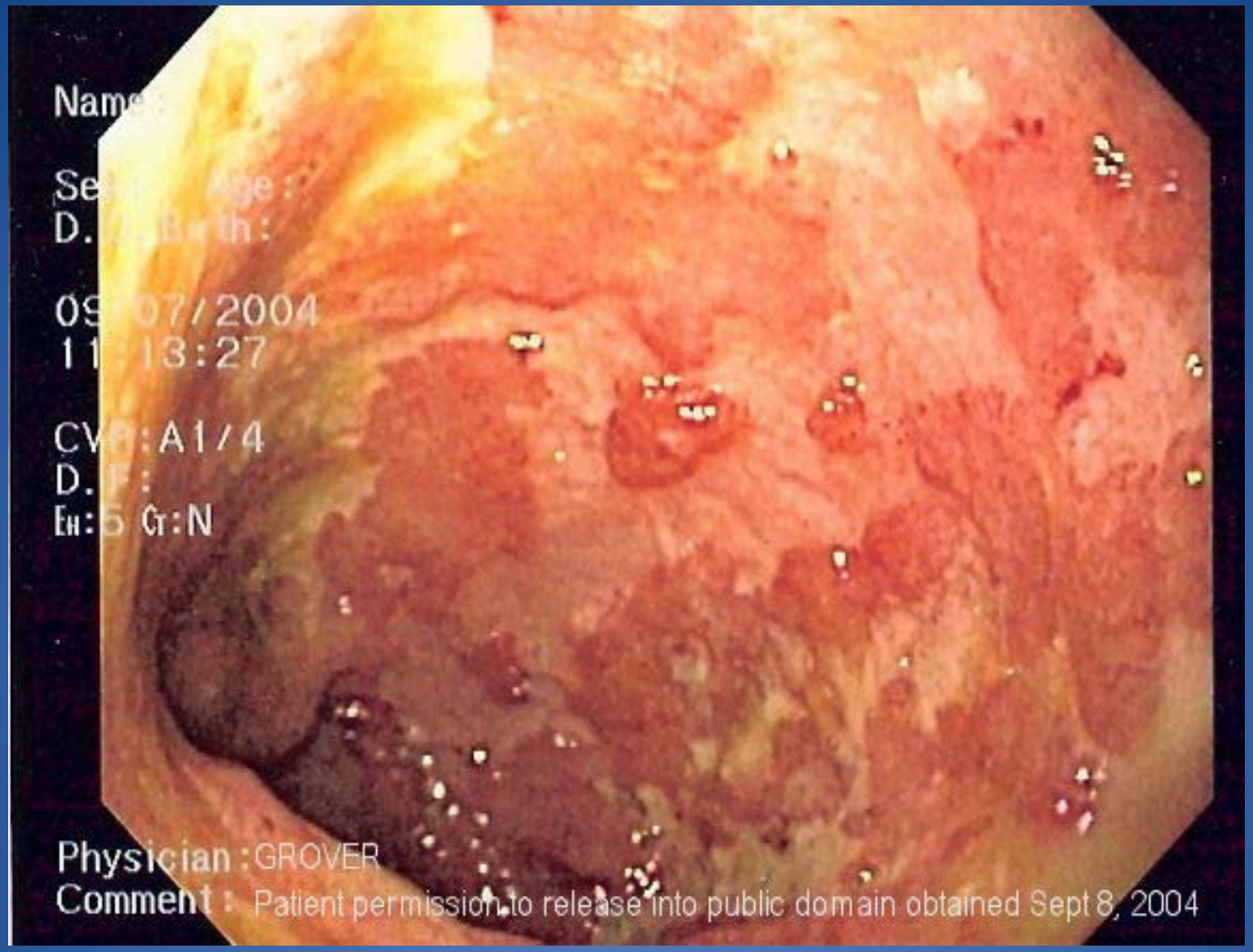


Mild Activity:
- < 4 stools daily
- No systemic disturbance
- ESR: NI

Moderate Activity: > 4 stools daily
- Minimal systemic effects

Severe Activity:
- ≥ 6 stools daily
- Bloody stools
- Fever
- Tachycardia
- Anemia
- ESR > 30 mm/hr

Hendriksen C, Kreiner S, Binder V. *Gut* 1985;26:158-163

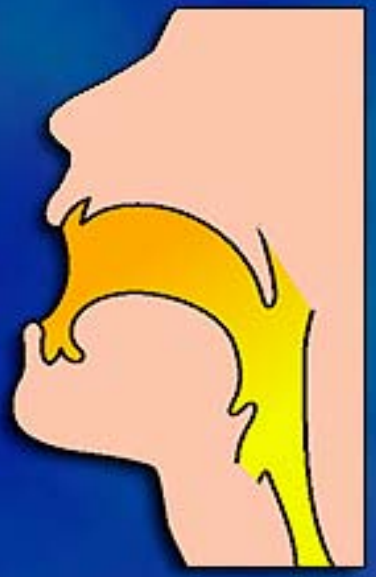


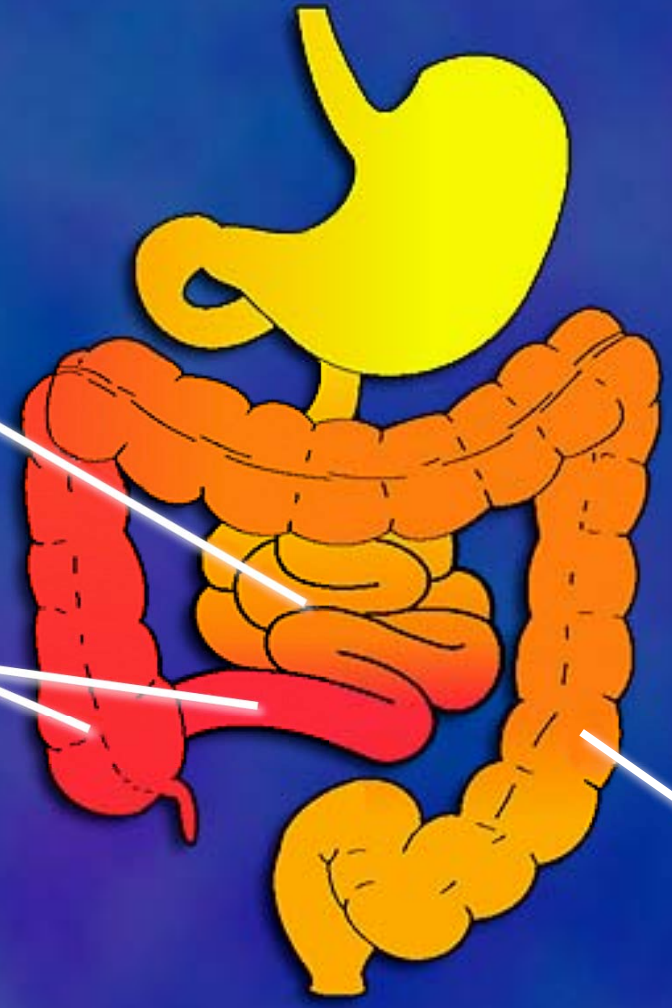
ulcerative colitis:the left side of the colon is affected
The image shows confluent superficial ulceration
and loss of mucosal architecture.

Presentation of CD

- Diarrhea
- Chronic abdominal pain and tenderness
- Weight loss
- Fever
- Perianal disease
- Symptoms vary with type and location of disease (stricturing, fistulizing)
- Extraintestinal manifestations

Crohn's Disease: Anatomic Distribution

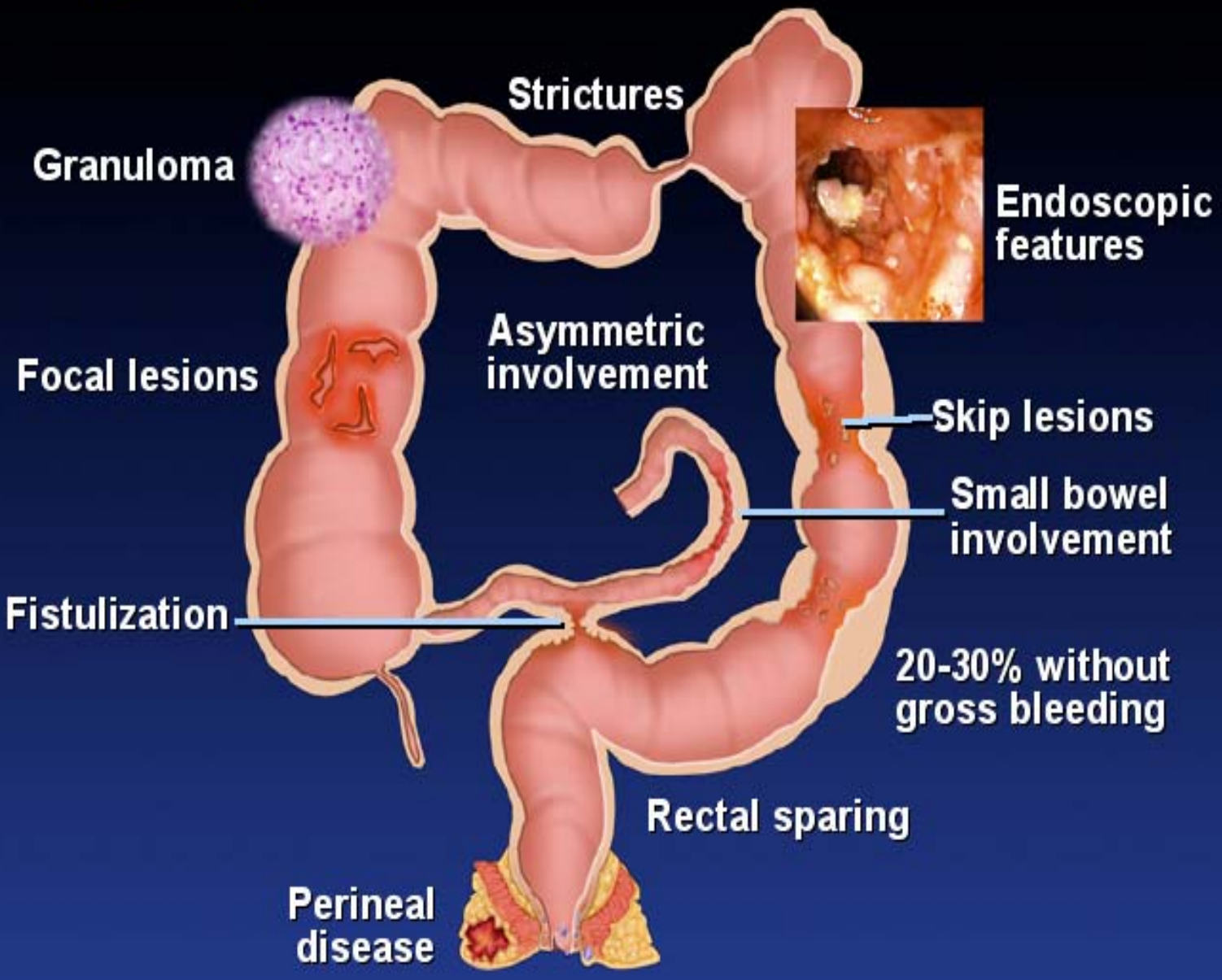


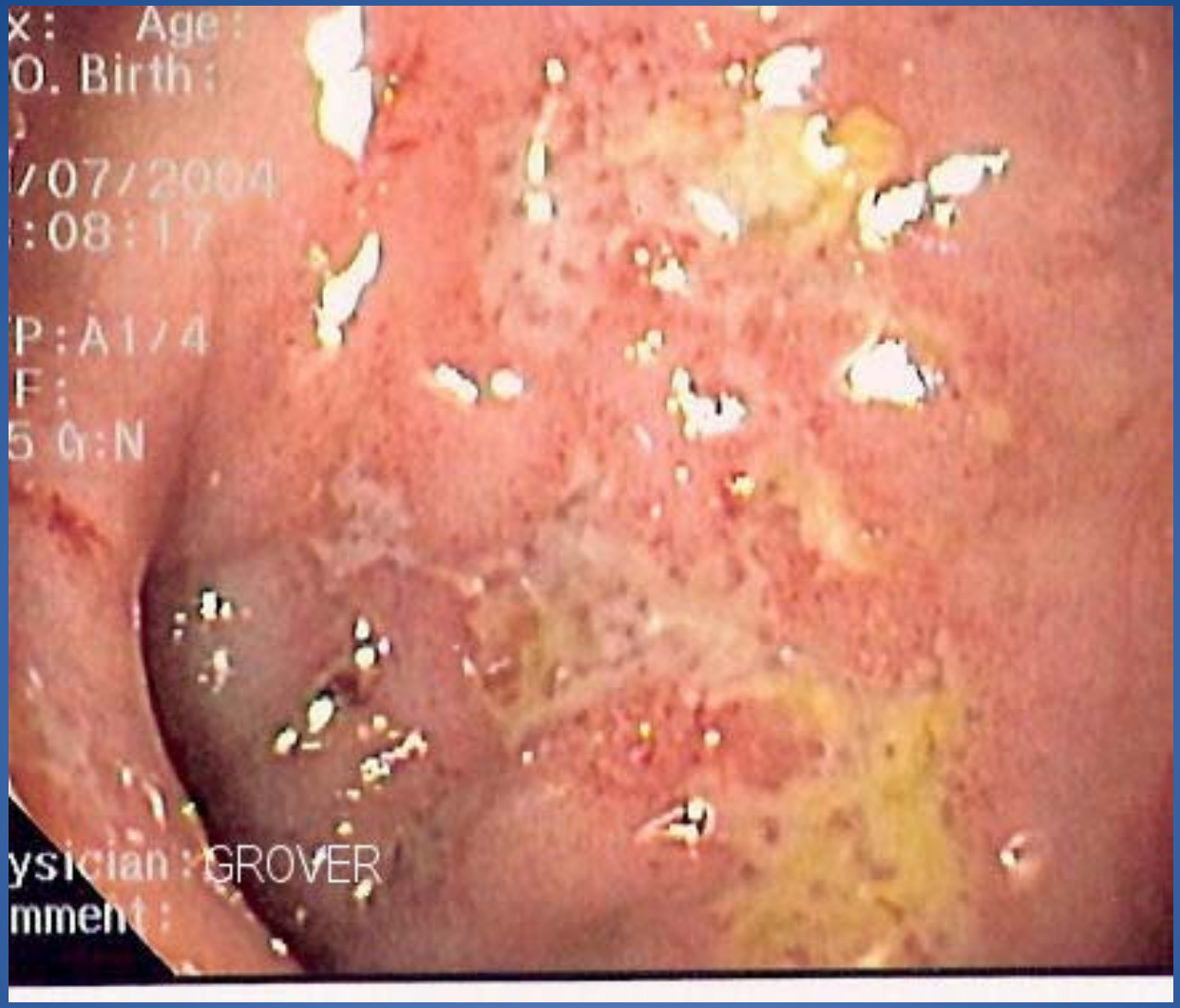


Freq of involvement

Most — Least

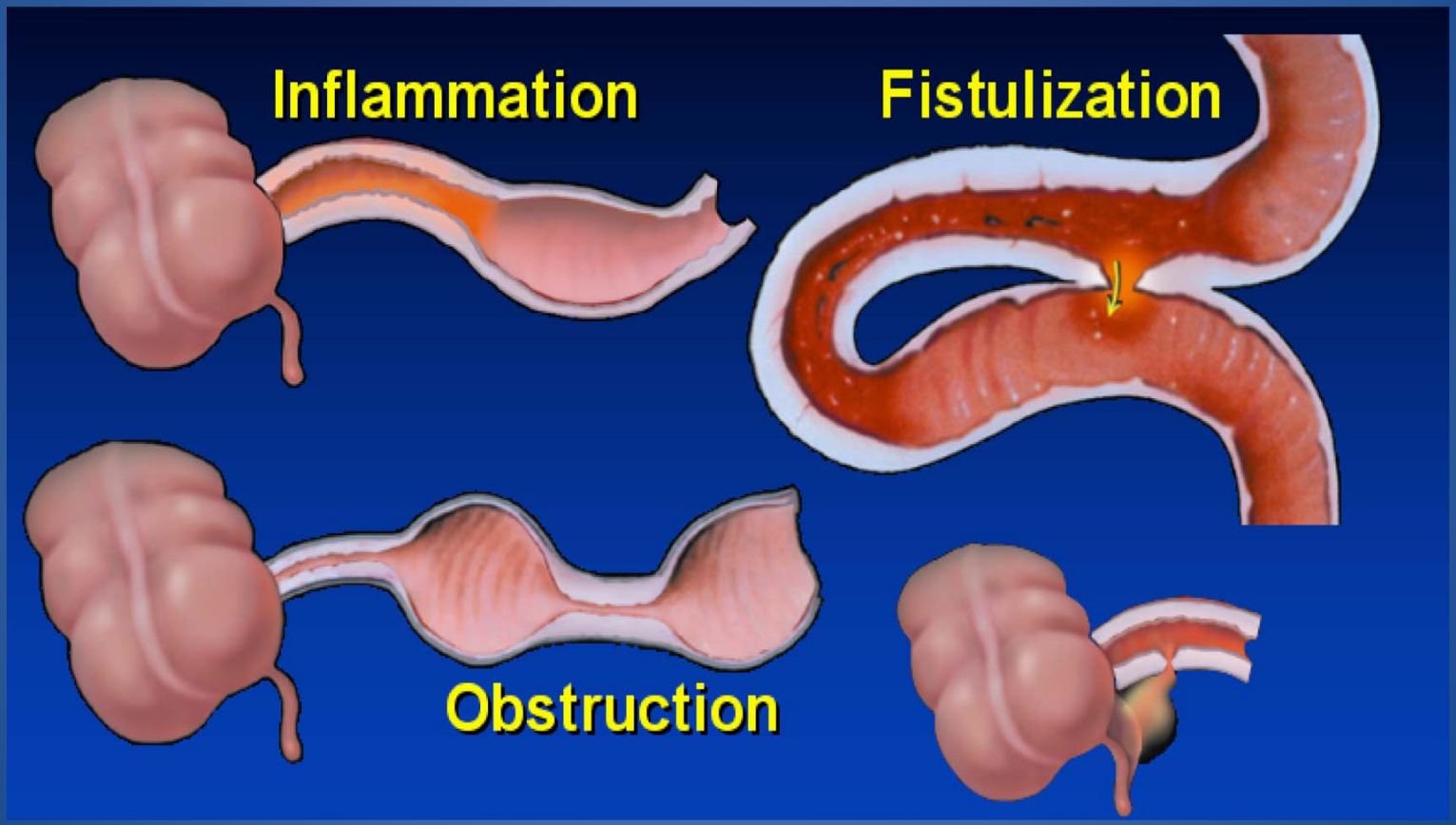
CD - Distinguishing Features



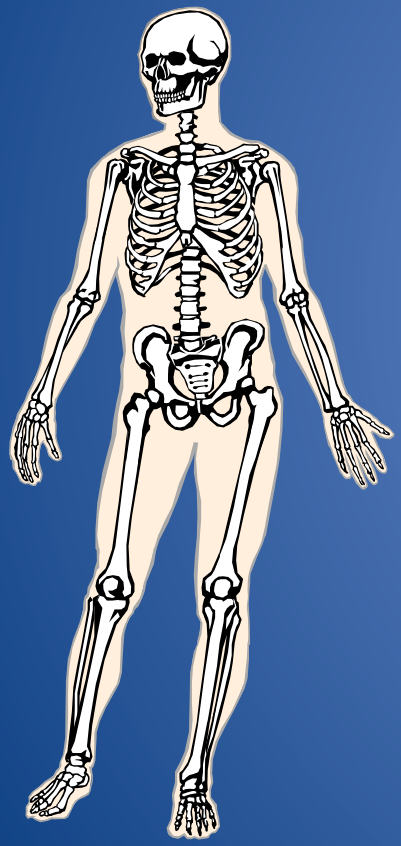


Serpiginous ulcer, a classic finding in Crohn's disease

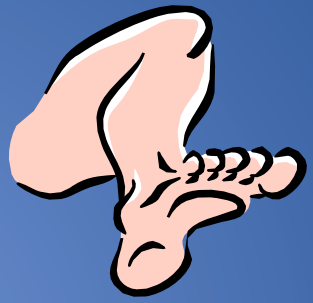
Phenotypes of Crohn's Disease



Extra-intestinal Manifestations of IBD

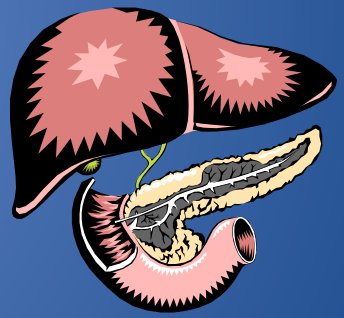


Skin



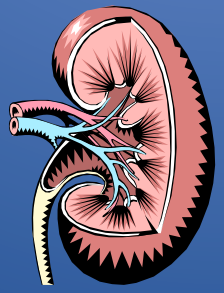
Eye

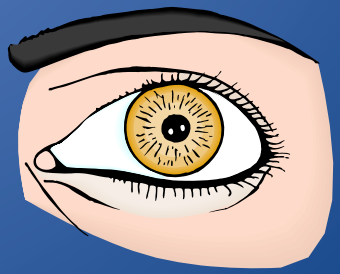
Bones and Joints



Kidney

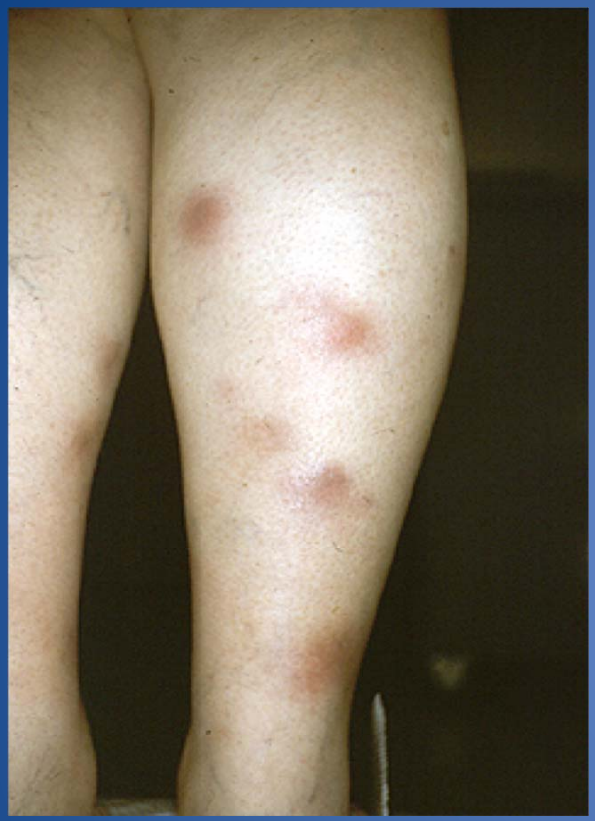
Hepatobiliary



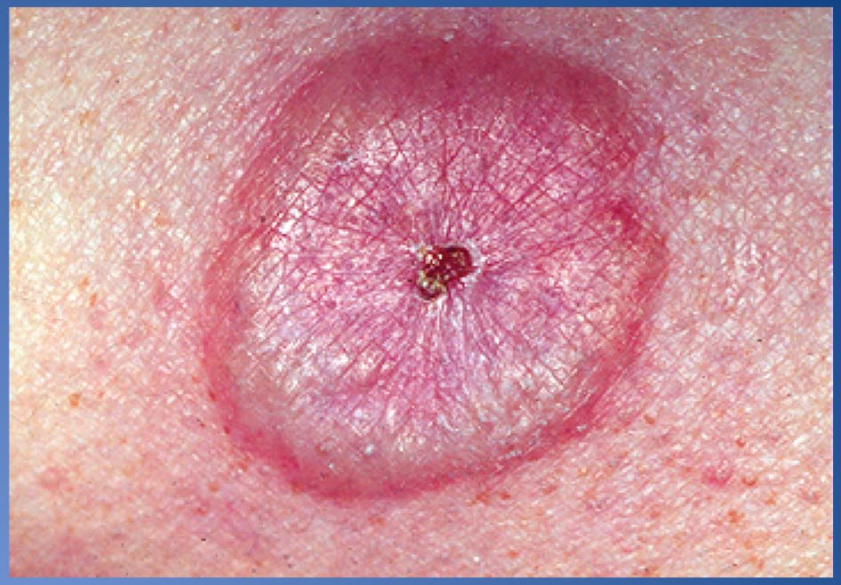


Extraintestinal Manifestations

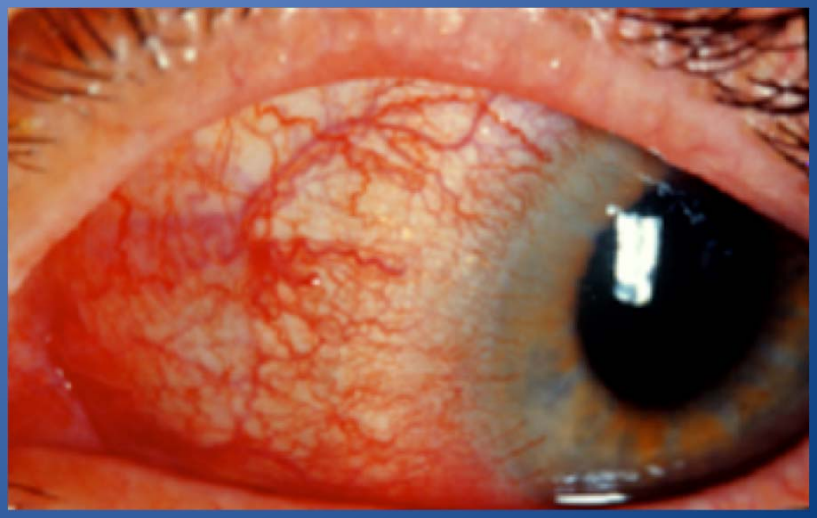
- Skin
  - Erythema nodosum
  - Pyoderma gangrenosum
  - Apthous ulcers
- Muskuloskeletal
  - Arthritis
  - Ankylosing spondylitis
  - Osteoporosis
- Hepatobiliary
  - Primary sclerosing cholangitis (UC)
- Ocular
  - Uveitis, iritis, episcleritis



Erythema nodosum

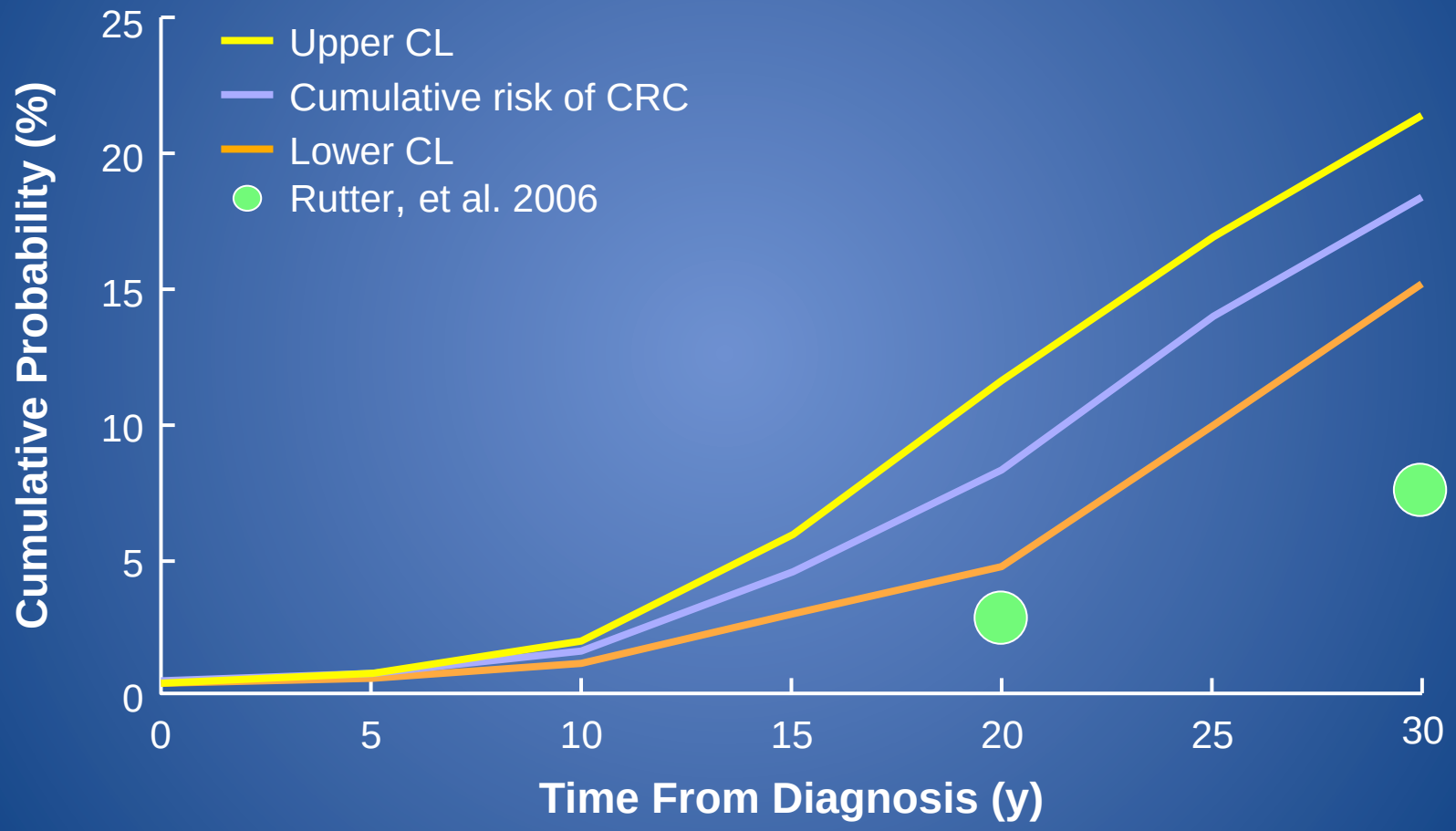


Pyoderma gangrenosum



Episcleritis

Cumulative Risk of Developing CRC in UC



CL=confidence limit.

Adapted from Eaden JA, et al. *Gut.* 2001;48:526-535 with permission from BMJ Publishing Group.

Rutter MD, et al. *Gastroenterology*. 2006;130:1030-1038.

Risks of Dysplasia or CRC in UC

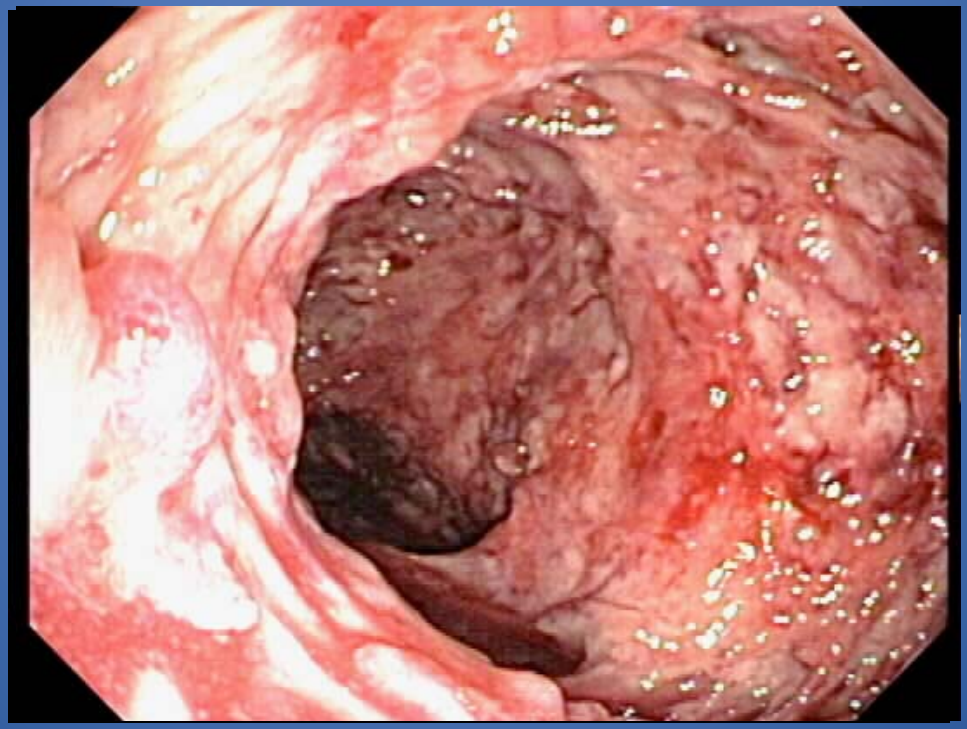
- Risk of CRC in UC
  - 2-5% after 10 years
  - 8-20% after 20 years
  - 18-40% after 30 years
- Risk Factors
  - Longer duration of disease
  - Greater extent of disease
  - Family history of CRC[1,2]
  - Primary sclerosing cholangitis[3]
  - Younger age of diagnosis
  - Backwash ileitis
  - Increased activity of disease[4,5,6]

[1]Askling et al. Gastroenterology. 2001. [2]Rubin et al. Clin Gastroenterol Hep. 2006.
[3]Lindberg et a I. Dis Colon Rectum. 2001.
[4]Rutter et al. Gastroenterology. 2004. [5]Moody et al. Gastroenterology, 2007.. [6]Rubin et al. DDW, LA 2006.

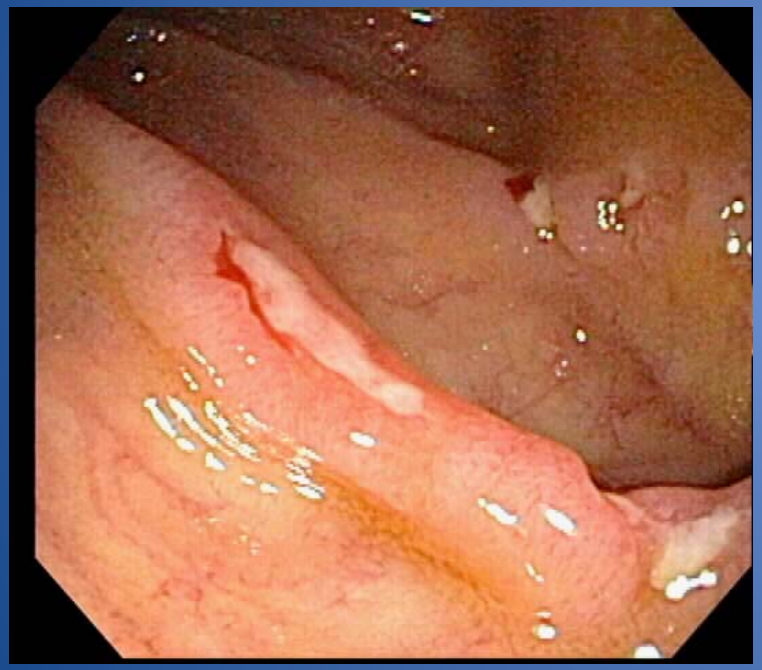
Diagnosis

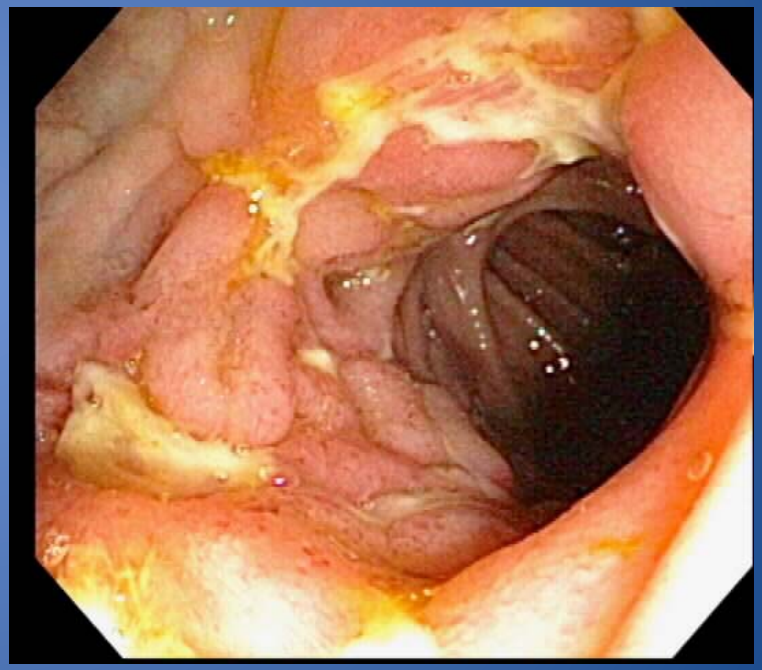
- Clinical diagnosis
  - History
  - Physical exam
  - Laboratories
    - CBC, Chem 20, stool studies, ESR, CRP
  - Radiology
    - X-ray, CT, MRI
  - Colonoscopy with biopsy
  - Capsule endoscopy

Ulcerative Colitis: Endoscopy

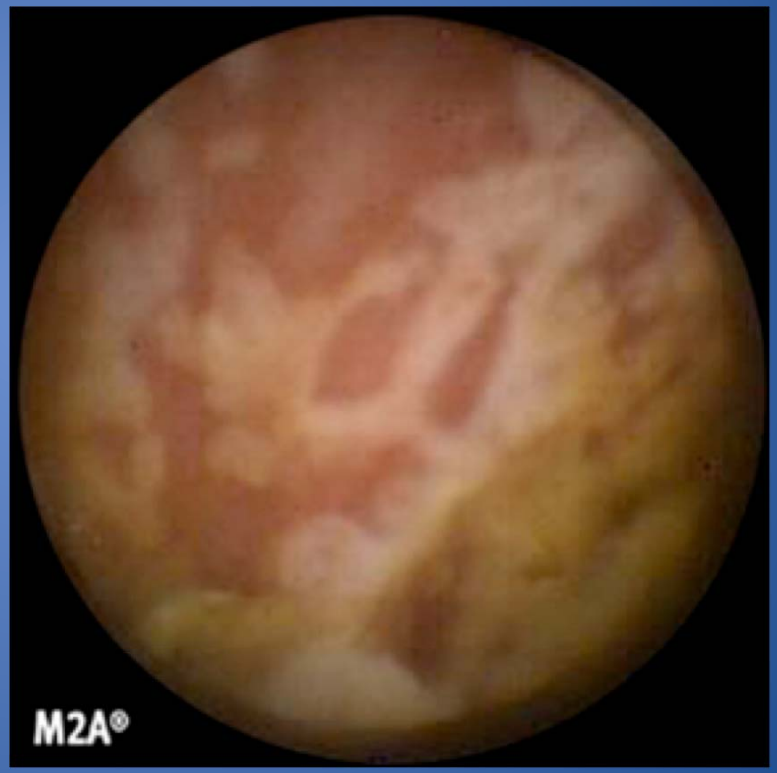


Crohn's Disease: Endoscopy





Capsule endoscopy



Crohn’s ulcers in small intestine

Histology

Ulcerative Colitis

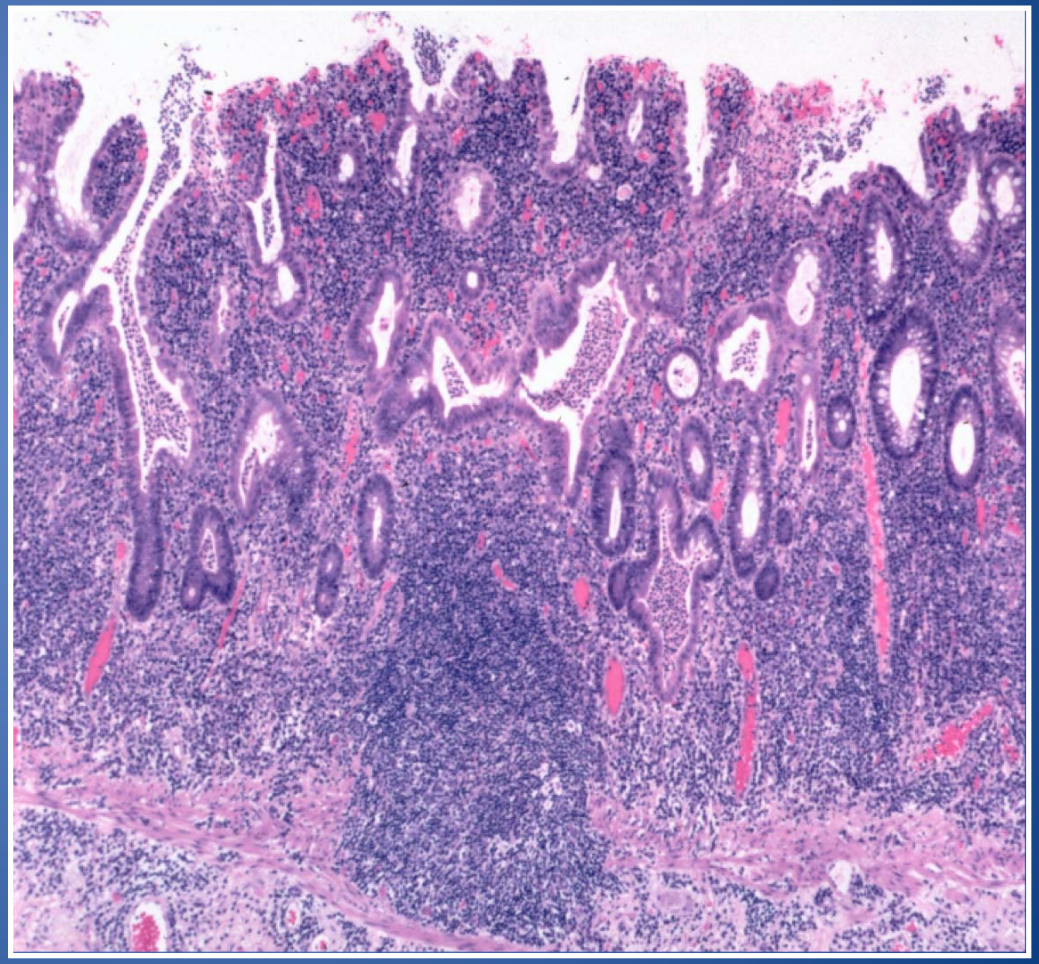
- Inflammation limited to mucosa and submucosa
- Submucosa often compressed
- Crypt abscesses common
- Goblet cells diminished
- Paneth cell metaplasia common
- Epithelioid granulomas absent in submucosa and deeper tissue levels

Crohn's Disease

- Transmural inflammation with lymphoid aggregates
- Submucosa expanded by inflammation and fibrosis
- Crypt abscesses less common
- Goblet cells often normal
- Paneth cell metaplasia rare
- Granulomas are frequent (40-60%)

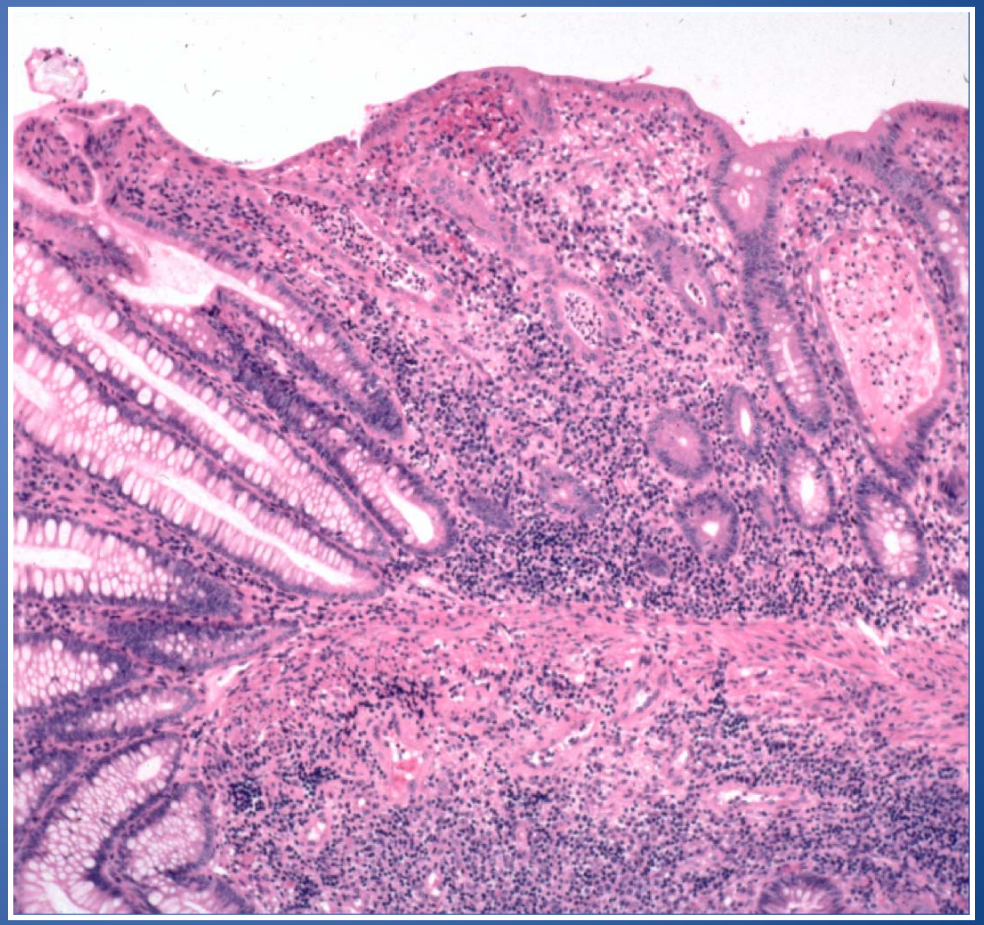
Active Chronic Ulcerative Colitis

- Inflammation is diffuse
- All biopsy fragments from a given region of colon are inflamed



Active Chronic Crohn's Disease

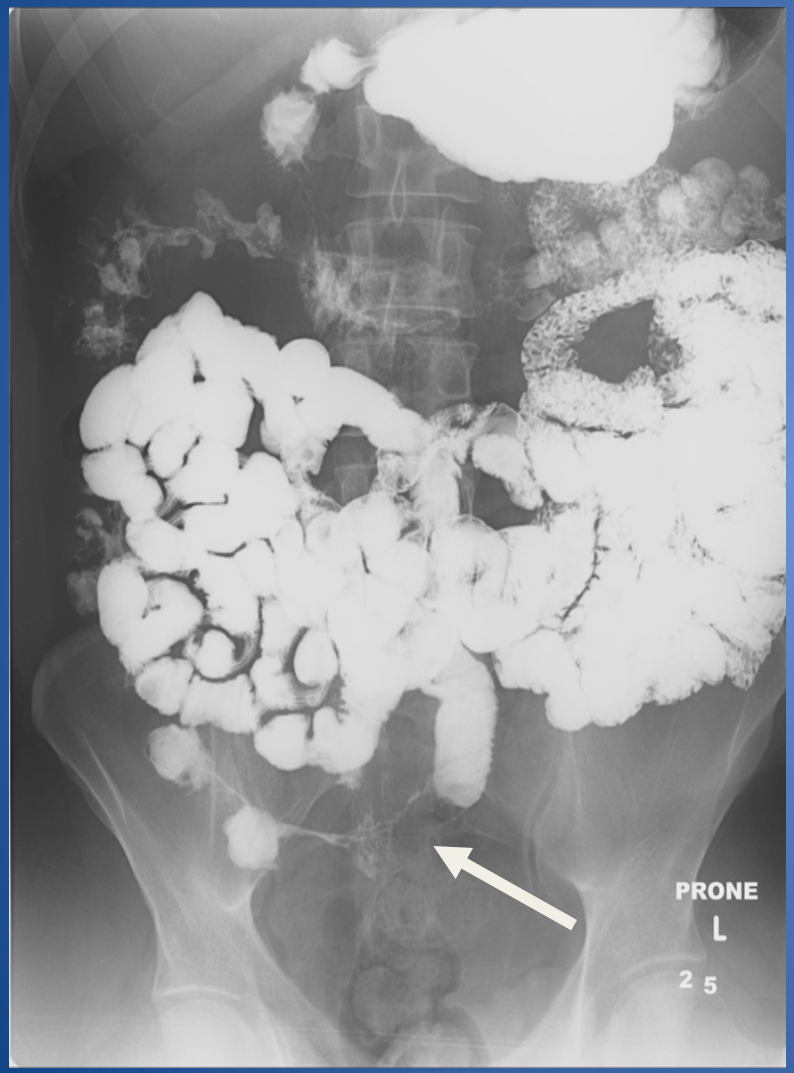
- Within single tissue fragments, activity is often focal
- Biopsies from a given region of bowel may have differing levels of activity
- These features are also seen in enteric and gastric disease

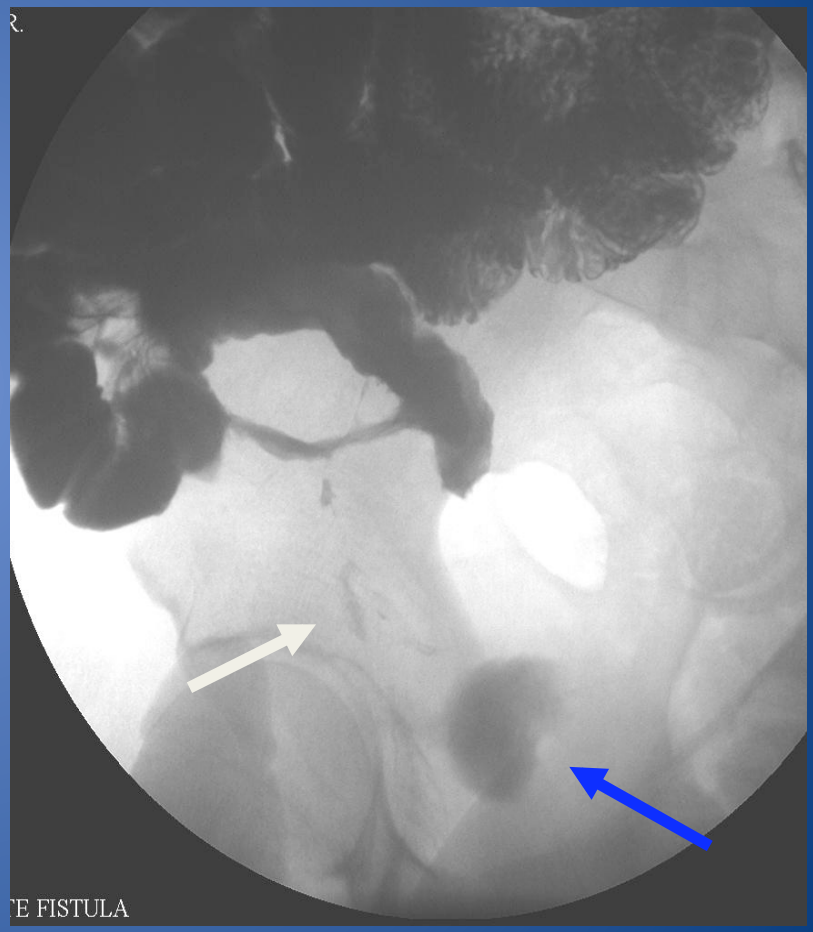


Imaging for Crohn Disease
Traditional Techniques

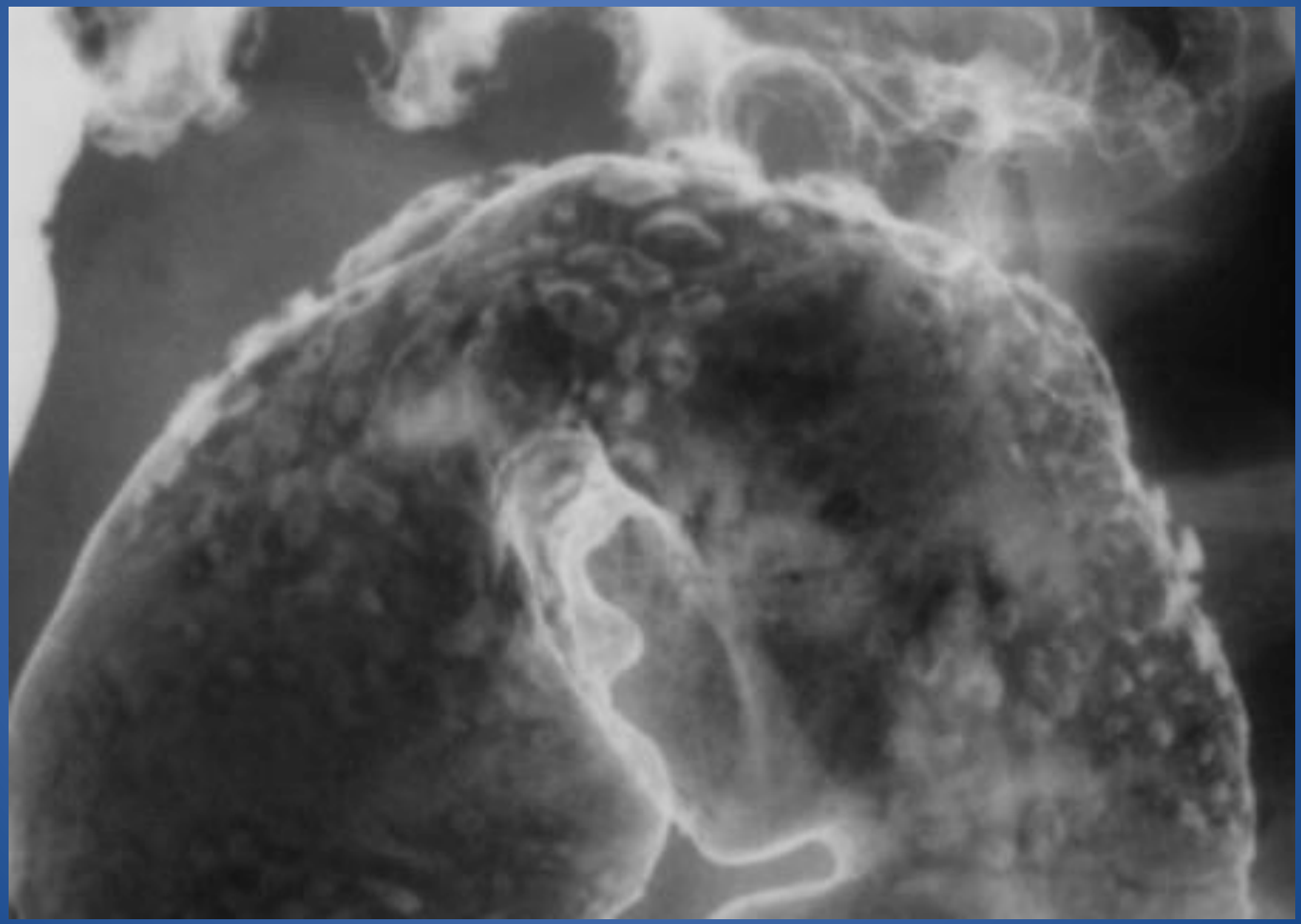
- Abdominal Radiographs
- Barium UGI
- Barium small bowel follow through
- Barium Enteroclysis
- Barium Enema

Ileo-vesical Fistula





Crohn’s Disease – Barium Enema



Imaging for Crohn Disease

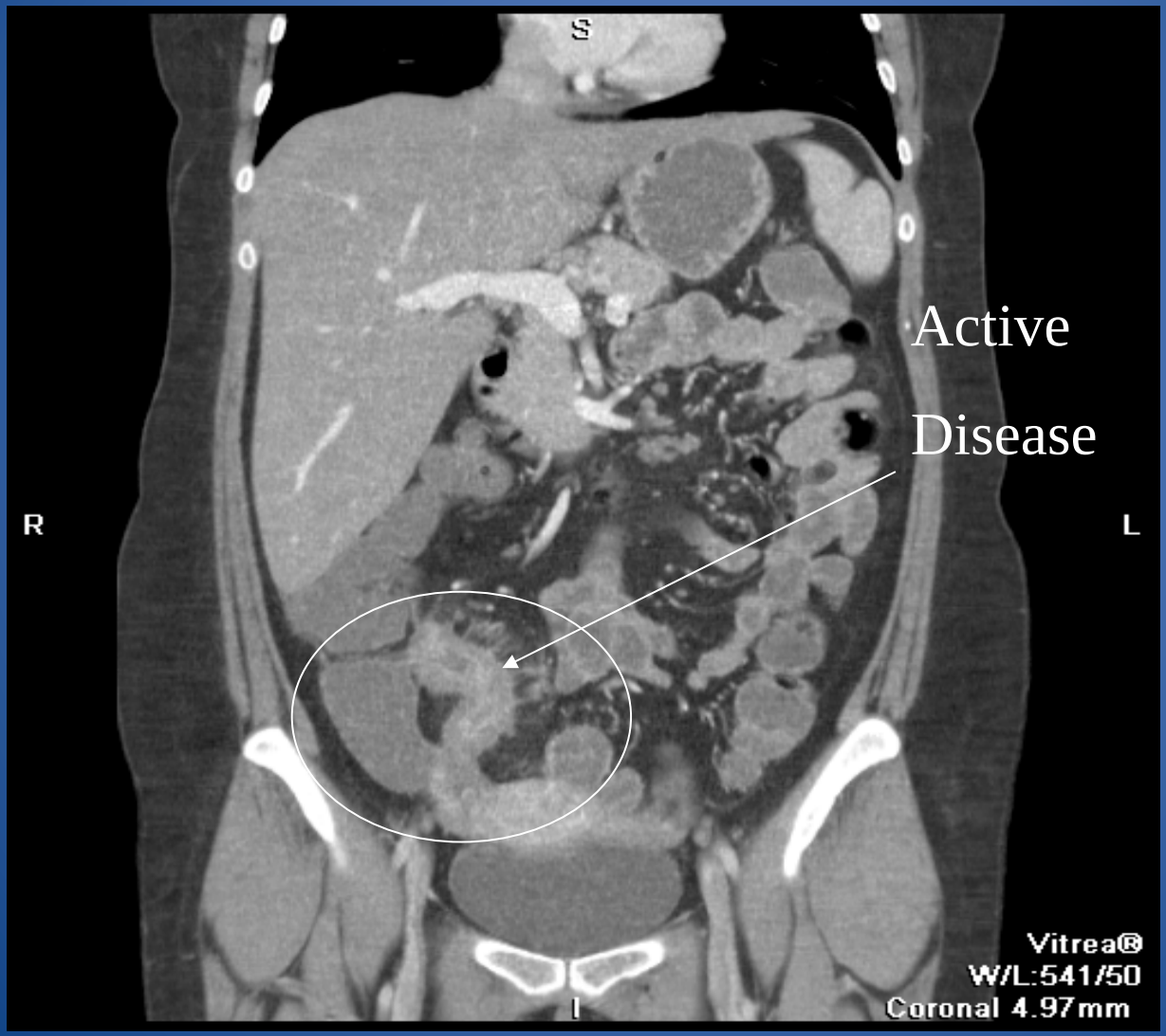
Newer Techniques

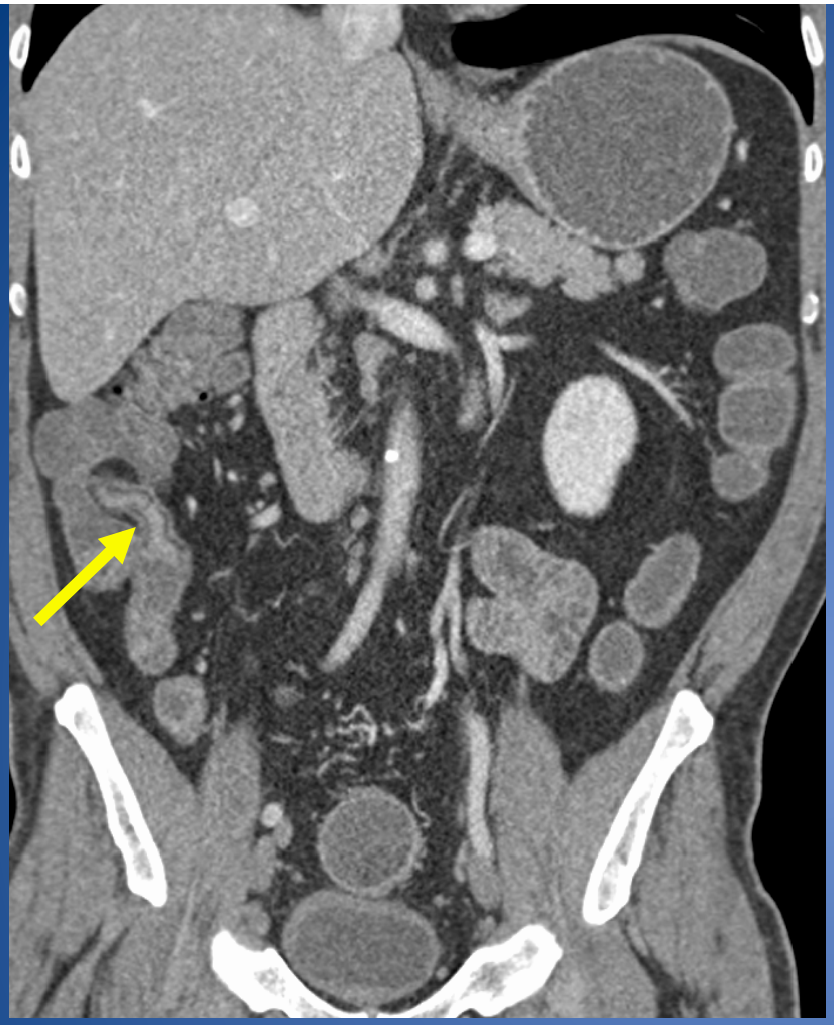
- CT
- CT Enteroclysis
- CT Enterography
- Magnetic Resonance
- Ultrasound
- Nuclear Medicine

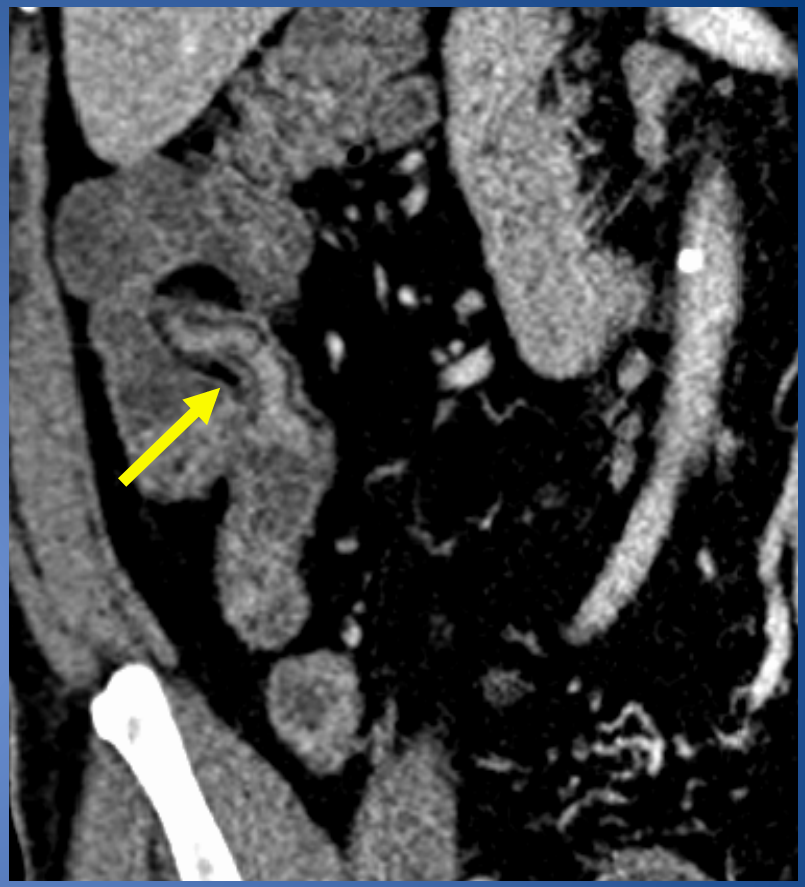
Imaging for Crohn Disease
Newer Techniques

- **CT Enterography**
  - High volume (1200ml) negative oral contrast (VoLumen) over 1 hour
  - improves small bowel distension c/w regular CT or SIFT
  - Give IV contrast to evaluate bowel wall
  - Use thin section multislice CT cuts to generate 3D coronal and saggital views also
  - Well tolerated by patients, no need for jejunal tube
-

CT Enterography



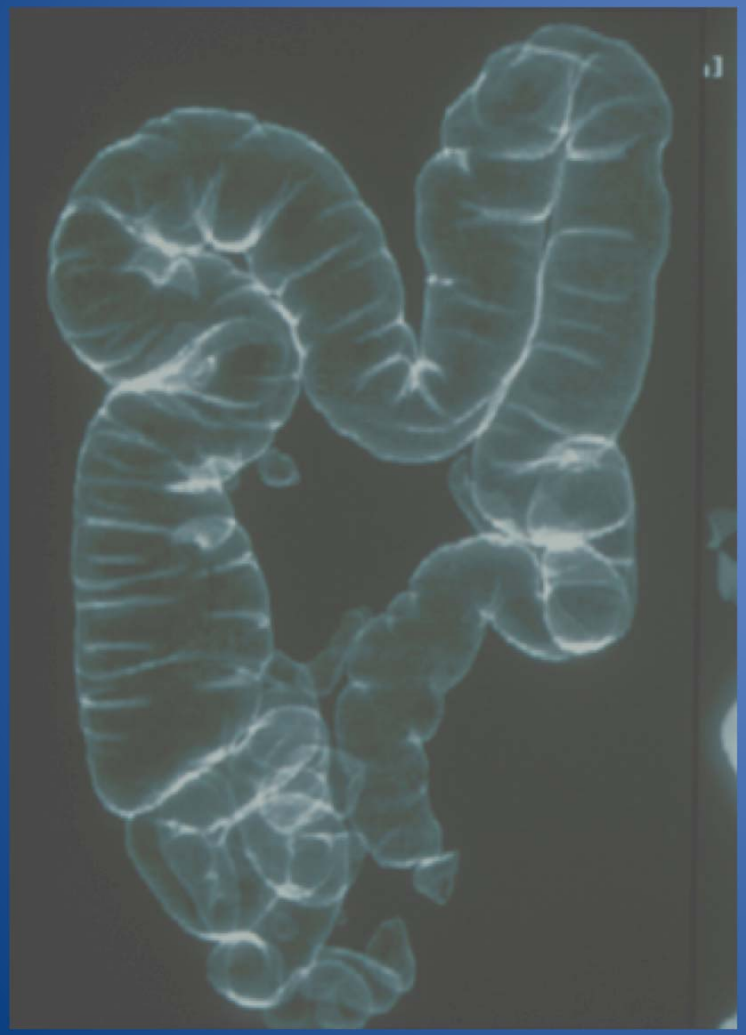


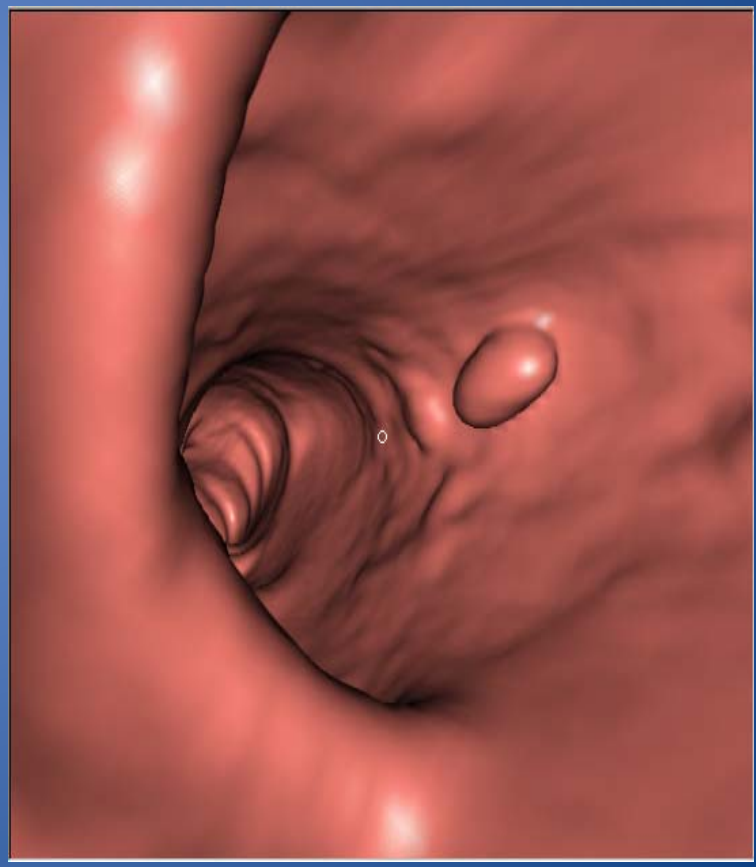


- Chronic Crohns in TI
- Fat in bowel wall

Imaging for Crohn Disease

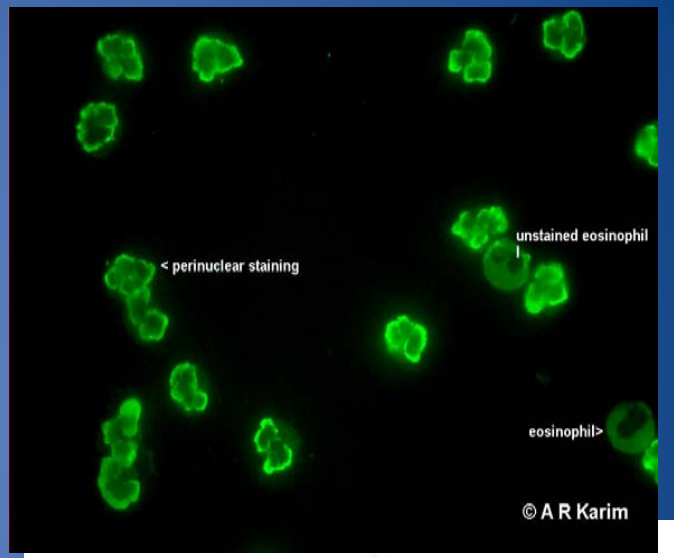
Virtual Colonoscopy





What are the Serological Markers in IBD?

- pANCA (perinuclear staining pattern)
  - Loss of perinuclear pattern after DNAase
  - Differentiate from the "other pANCAs"
    - Antibody against myeloperoxidase
    - Antibody against cathepsin G, elastase, lysozyme, and lactoferrin
- ASCA (anti-*Saccharomyces cerevisiae*)
  - Both IgG and IgA
  - Recognize mannose in the cell wall mannan of *Saccharomyces cerevisiae*



IBD Serology - Prometheus

- ASCA: The "Crohn's Disease Ab"
  - + in ≈ 60% of CD[1-3]
  - IgA + IgG vs. cell wall of *S. cerevisiae* *(yeast)*
- pANCA: The "Ulcerative Colitis Ab"
  - + in ≈ 40-80% UC, 2-28% CD ("UC-like" CD)[4]
  - Newer assay more specific for UC
    - **Loss of perinuclear stain after DNAse**
- **Not 100% diagnostic!**

What are the Serological Markers in IBD-2?

- Omp C
  - IgG only
  - Recognize outer membrane porin C protein in *E. coli*
- I2
  - IgA only
  - Recognizes novel homologue of bacterial transcription-factor families from a *Pseudomonas fluorescens*-associated sequence
- Cbir 1 flagellin
  - IgG

Use of IBD Serologies

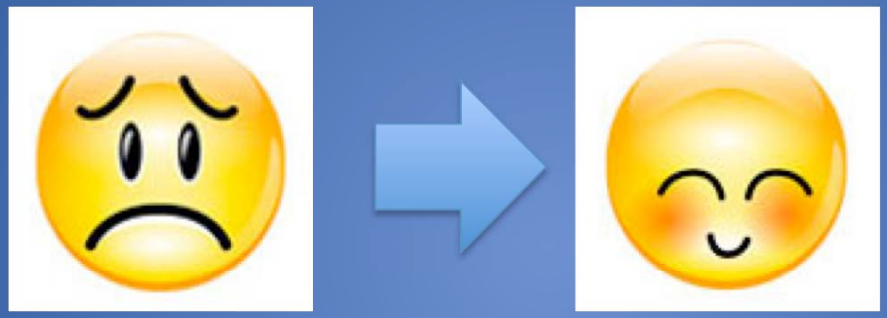
- pANCA and ASCA are specific for UC and CD respectively
- Neither pANCA nor ASCA are sensitive enough to exclude IBD
- In patients with IC, available serological markers do not accurately predict the subsequent disease course
- Antibody profiles can predict disease behavior in IBD

Outline

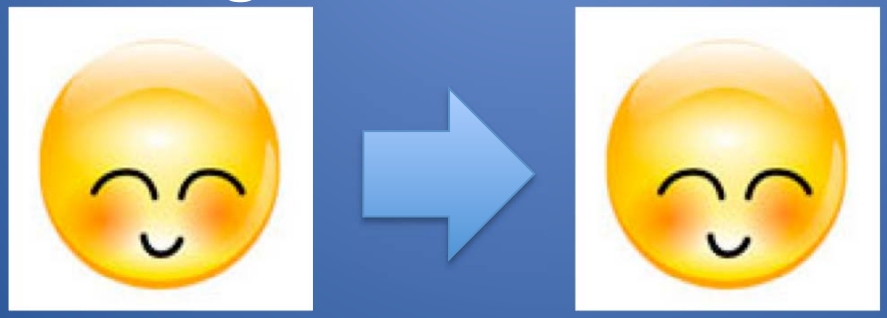
- Patient Presentation
- Definition
- Epidemiology
- Clinical Presentation
- Treatment Options
  - Goals of Therapy
  - Medications
  - Need for New Therapies

Goals of Therapy for IBD

- Inducing remission



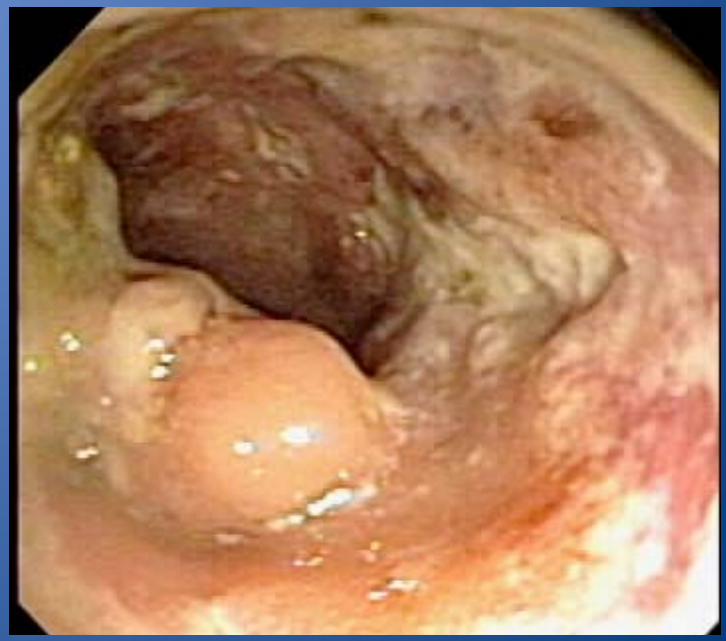
- Maintaining remission



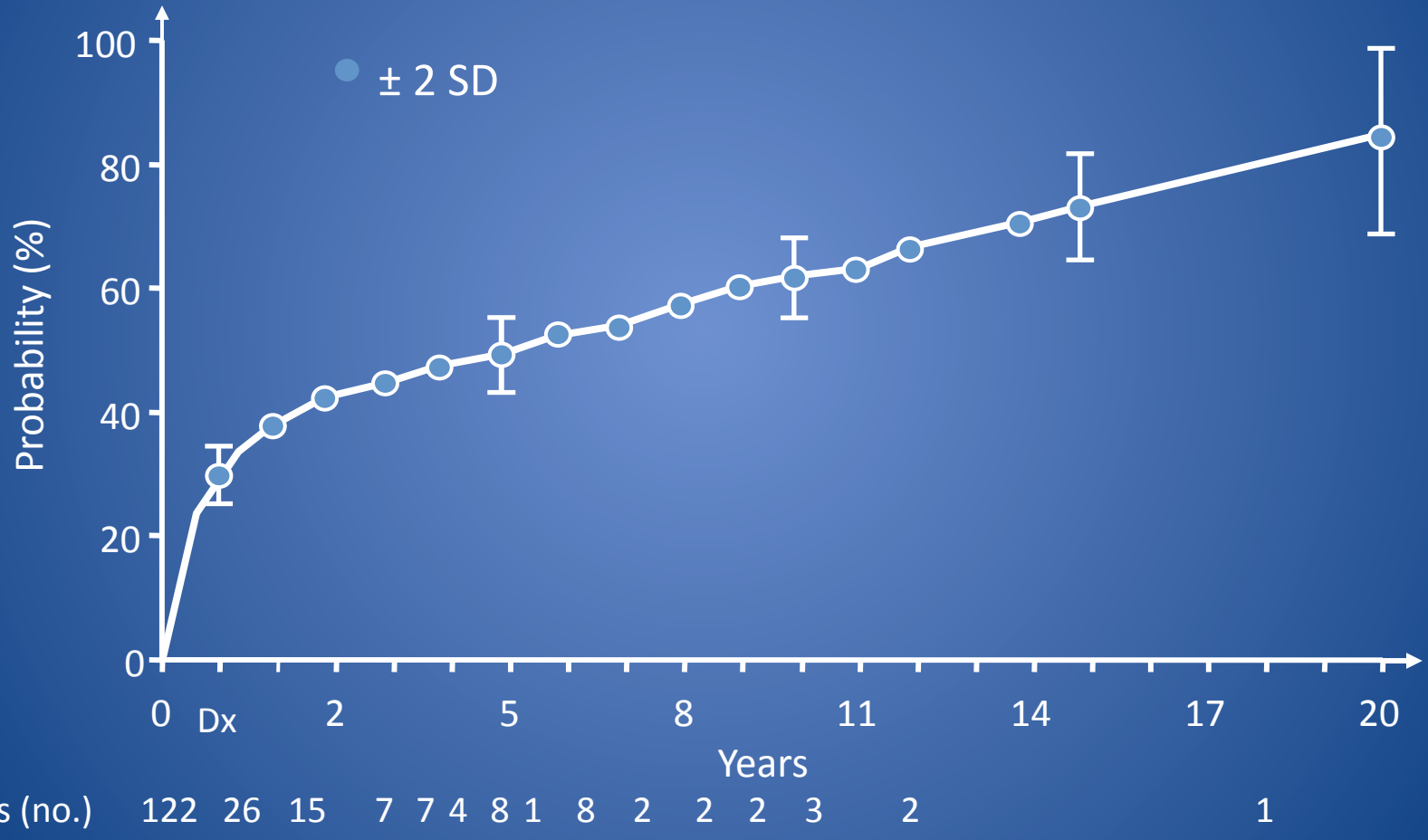
Other goals: quality of life, maintaining nutrition, avoidance of surgery

Goals of Therapy in IBD

- **Induce Remission of Active Disease**
- **Maintenance of Remission**
- **Maintain/Restore Nutrition**
- **Avoid Surgery**
- **Avoid Complications**
  - **Therapy-related**
  - **Disease-related**
- **Quality of Life**

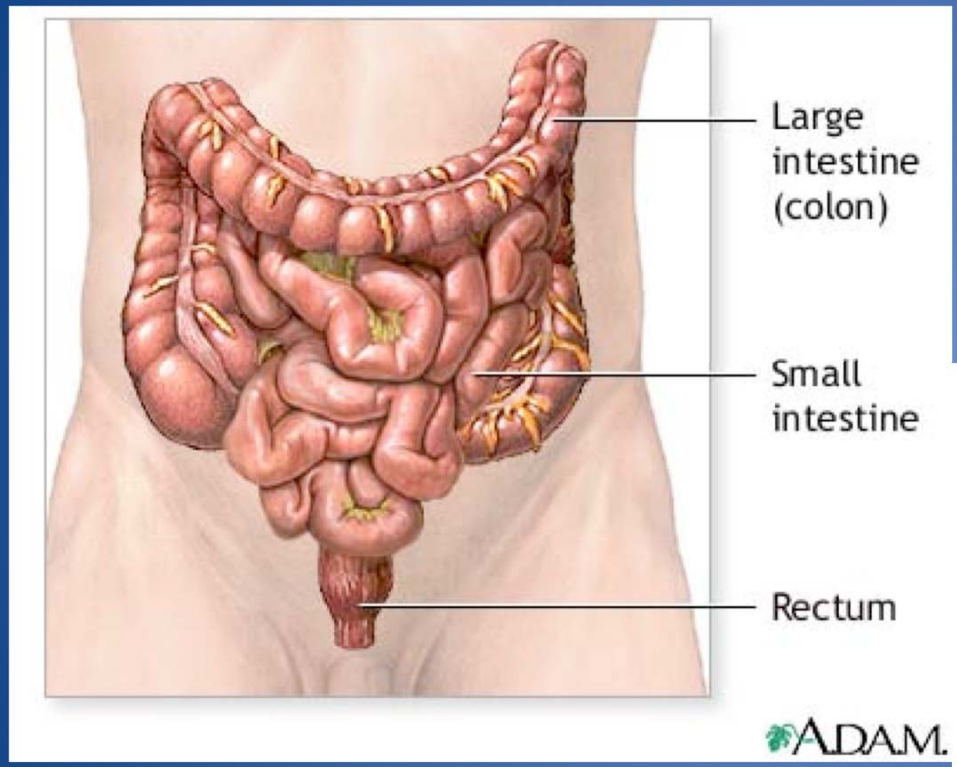


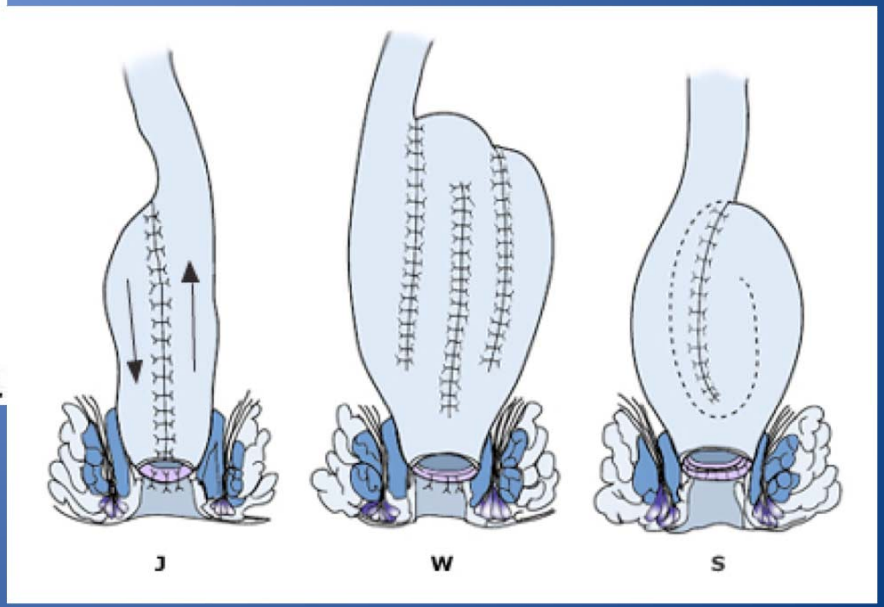
Cumulative Probability of Surgical Intervention in CD



Munkholm P et al. *Gastroenterology*. 1993;105:1716.

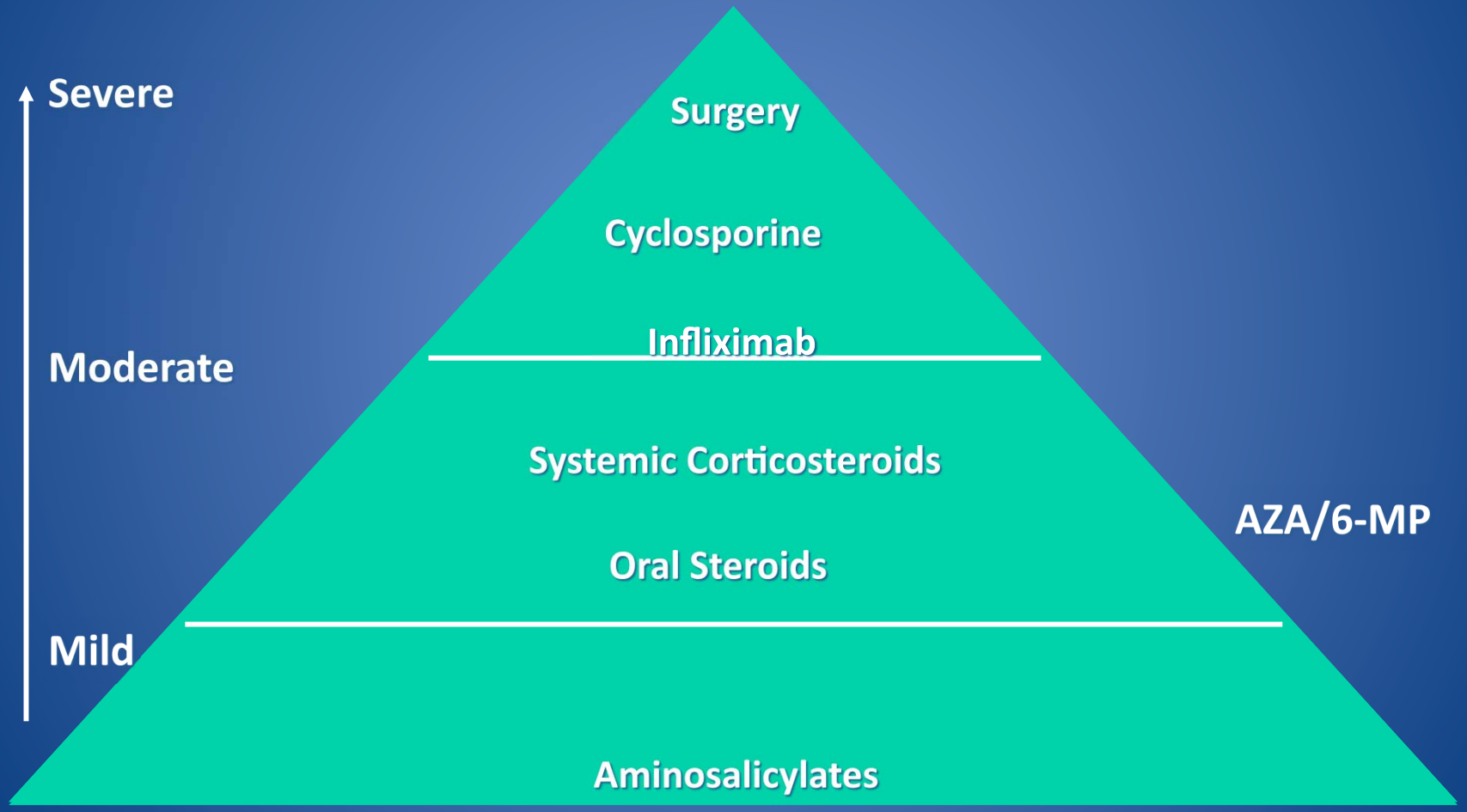
Surgery



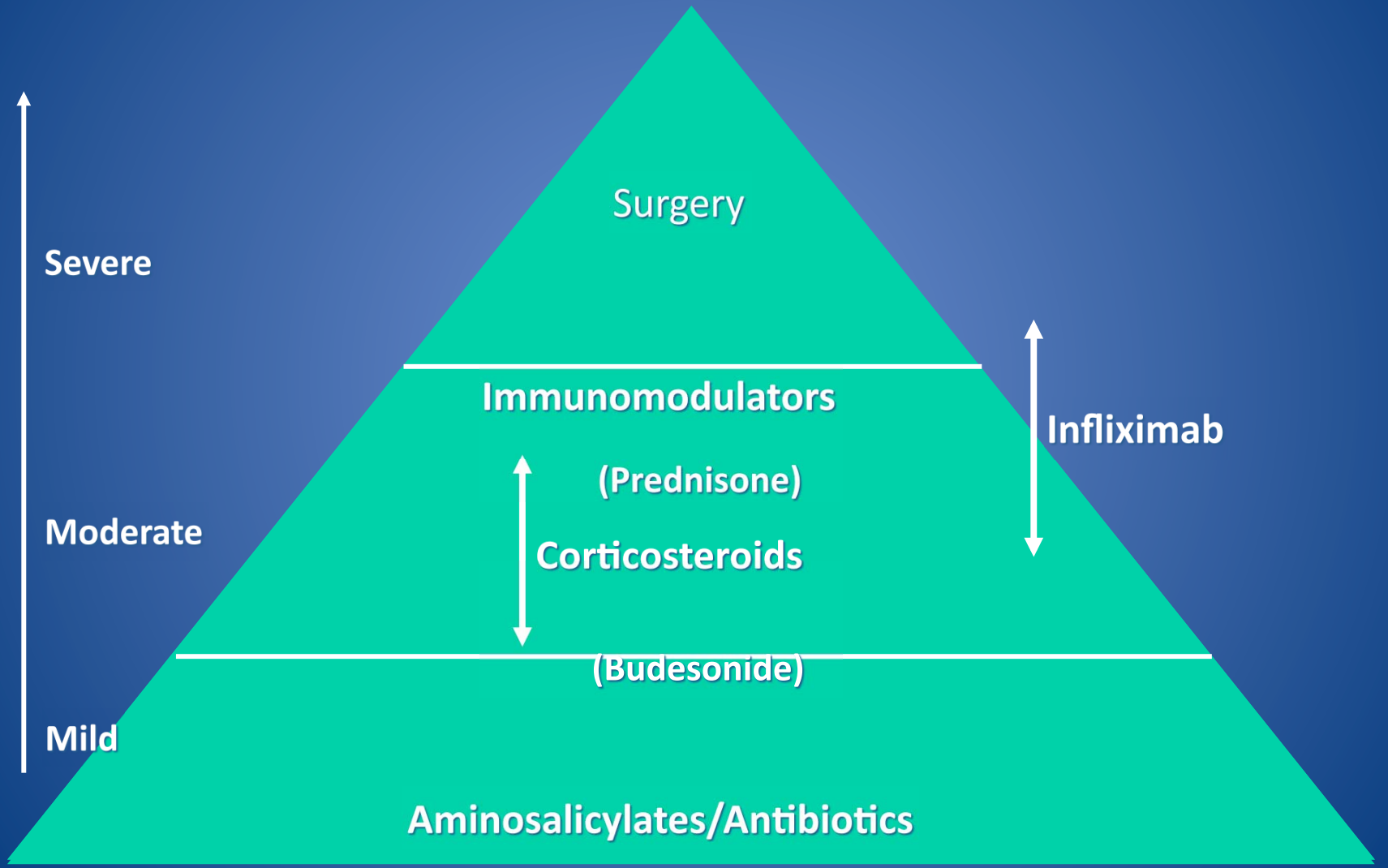


Ileal pouch - UC

Therapeutic Pyramid for Active UC



Therapeutic Pyramid - Crohn's Disease



Therapies

Class	Examples	Side Effects
5-ASA (mesalamine)	Asacol, pentasa, colazol, etc.	Nausea, diarrhea, HA, nephritis
Antibiotics	Flagyl, cipro, rifaximin	C. diff, neuropathy, nausea
Steroids	Budesonide, prednisone	Diabetes, cataracts, mood, skin, osteoporosis, etc.
Immunomodulators	Azathioprine, 6-MP, Mtx	Leukopenia, hepatitis, cancer
Anti-TNF	Infliximab, certolizumab, adalimumab	Infections, liver, malignancy
Anti-integrin	Natalizumab	Infections, PML

Traditional Therapies

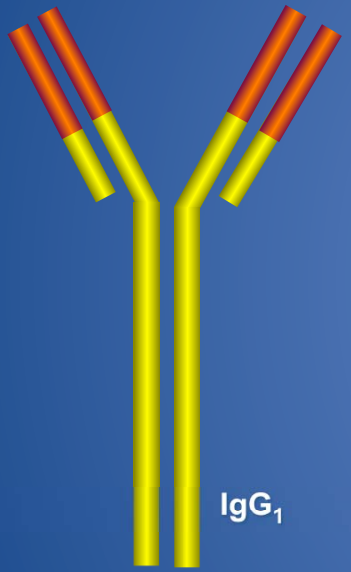
- Mesalamine (5-ASA)
  - Oral or Rectal
- Steroids (IV or Oral)
- Immunomodulators
    - Azathioprine (Imuran)
    - 6-Mercaptopurine (6-MP)
    - Methotrexate

Newer Therapies

- Advent of biologic agents dramatically changed IBD treatment
- Biologics
  - Specifically target mediators of inflammation
  - Anti-TNF Ab
    - Anti-Tumor Necrosis Factor Alpha Antibodies

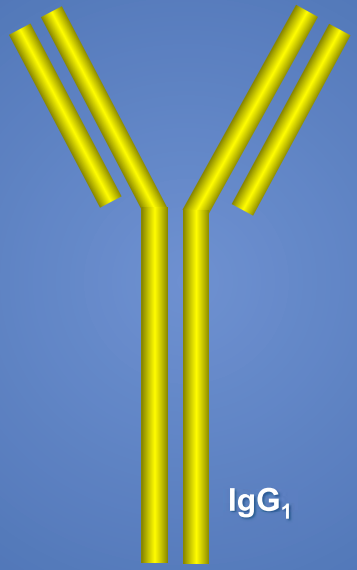
Construct of Anti-TNF-α Biologic Agents

Infliximab



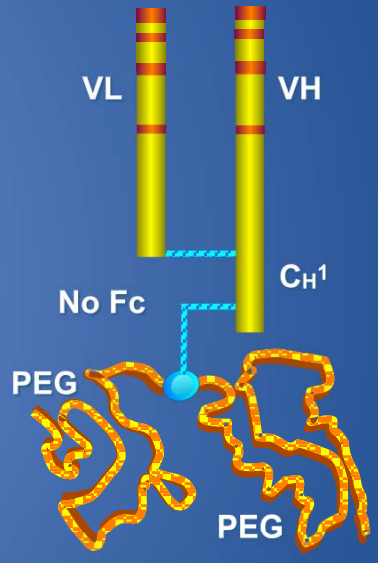
Chimeric monoclonal antibody (75% human IgG_1 isotype)

Adalimumab



Human recombinant antibody (100% human IgG_1 isotype)

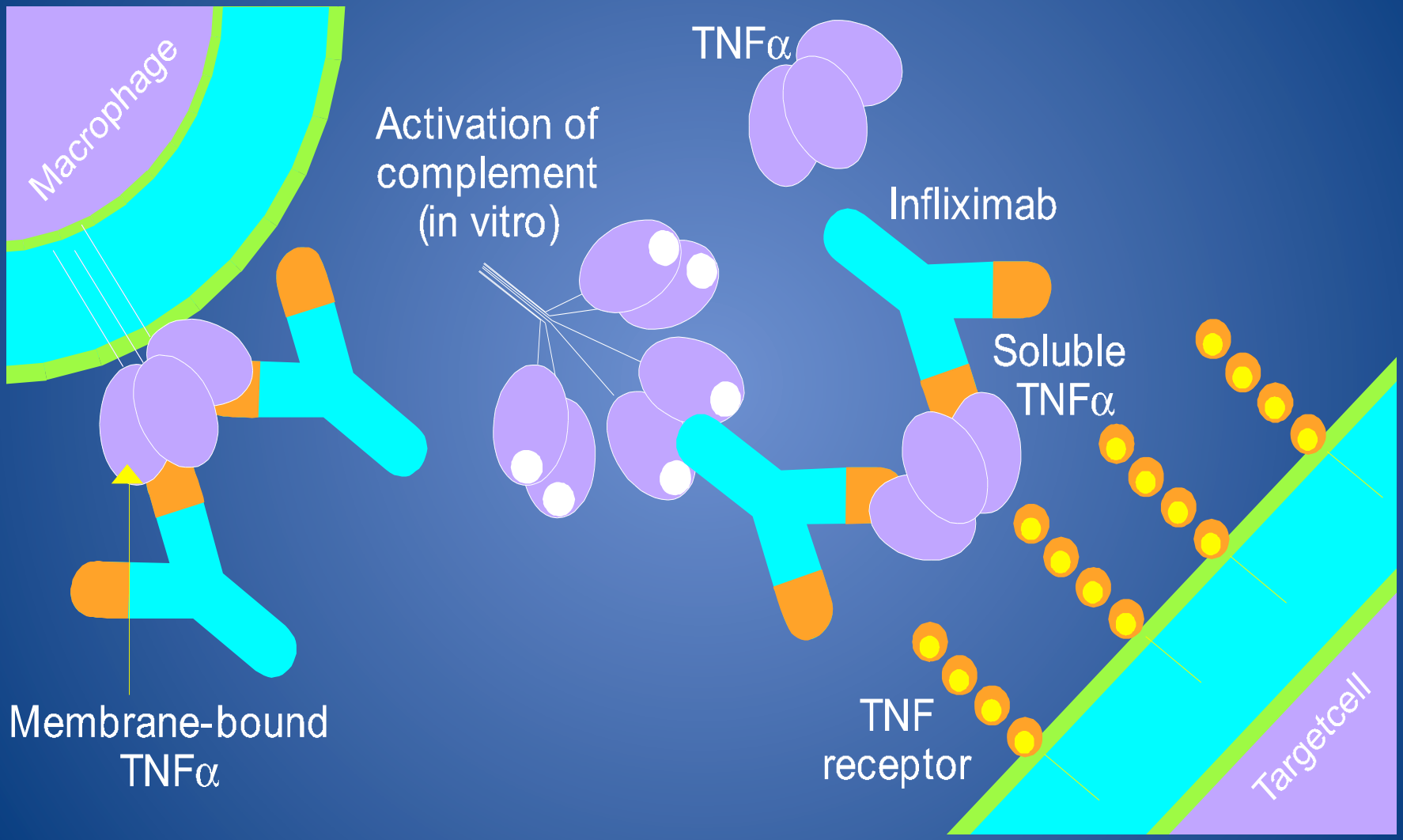
Certolizumab Pegol



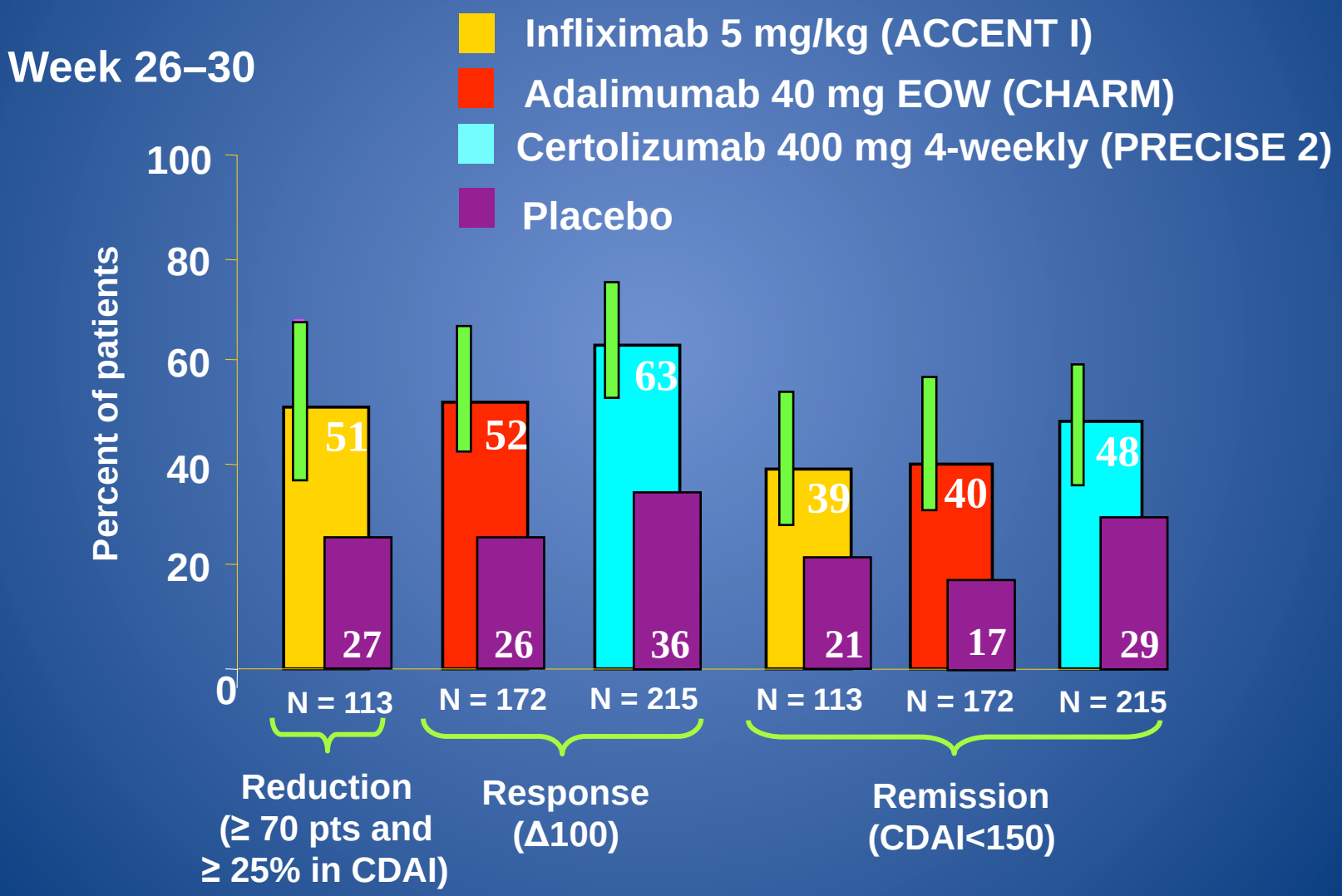
Humanized Fab' fragment (95% human IgG_1 isotype)

Mouse
Human
PEG, polyethylene glycol.

Infliximab: Mechanism of Action

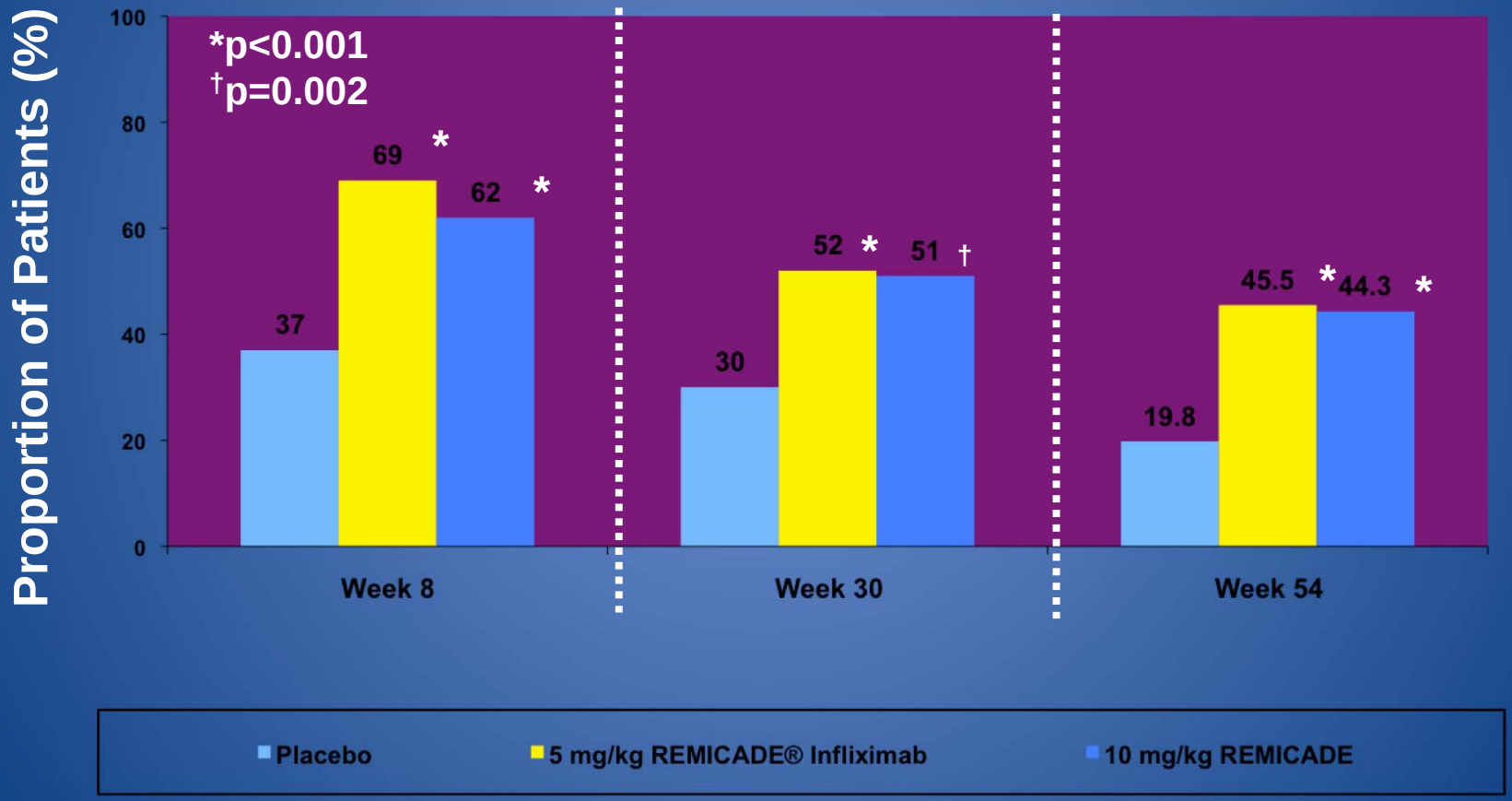


Maintenance of Remission in CD: *Different Studies, Similar Efficacy*



ACT 1

Infliximab therapy for UC

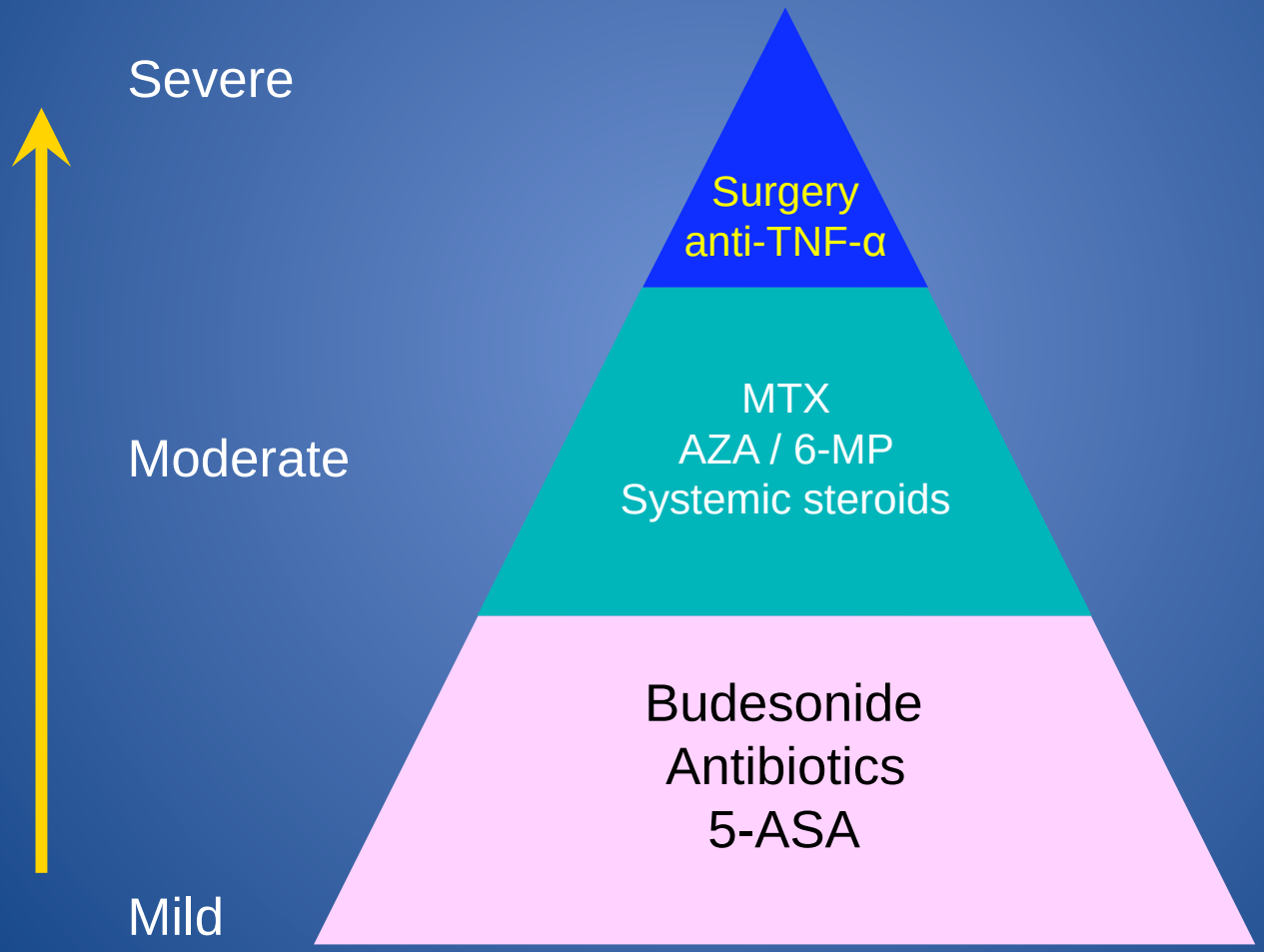


Rutgeerts P et al. *N Engl J Med*. 2005;353(23):2462-2476.

Need for New Therapies?

- Lack of sustained remission
  - Loss of response to Anti-TNF agents
- Need to change natural history of disease
  - Avoidance of surgery
  - Avoidance of long-term complications

Current “Therapeutic Pyramid” for Crohn's disease



Adapted from: Hanauer et al, Am J Gastroenterol 2001; 96: 635

Crohn's Medical Treatment

Induction

Sulfasalzine (colitis)/
Budesonide (ileal/R.colitis)➔
Oral prednisone➔
Anti-TNF

Maintenance

Azathioprine/6-MP
Anti-TNF

Percent not achieving remission:

5ASA: 57-68%

Steroids: 40-49%

Infliximab: 60%

Percent not maintained in remission:

AZA: 34%

Infliximab: 57%

Katz, *J Clin Gastroenterol* 2007

Ulcerative Colitis Medical Treatment

Induction

Sulfasalzine/mesalamine ➔

Oral prednisone ➔

Anti-TNF ➔

Cyclosporine/tacrolimus

Maintenance

Sulfasalzine/mesalamine

Azathioprine/6-MP

Anti-TNF

Percent not achieving remission:

5ASA: 44%

Steroids: 30-60%

Anti-TNF: 61-74%

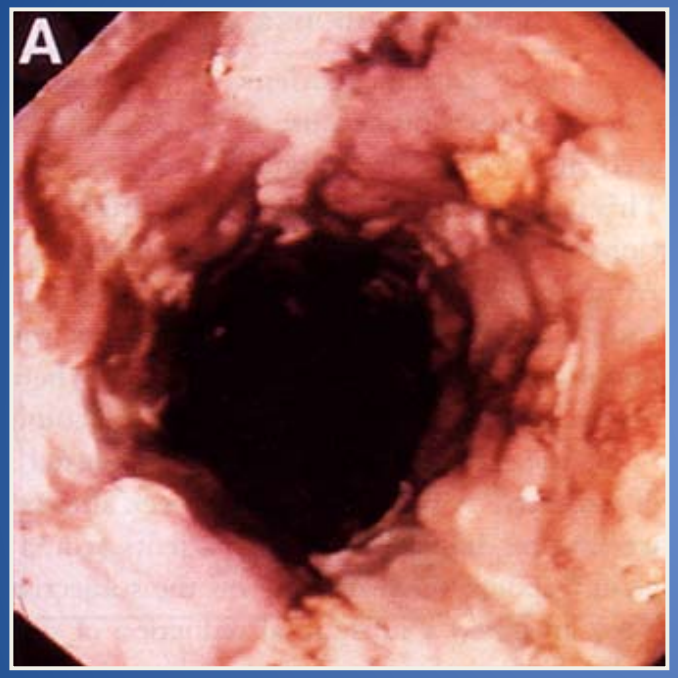
Percent not maintained in remission:

AZA: 40-60%

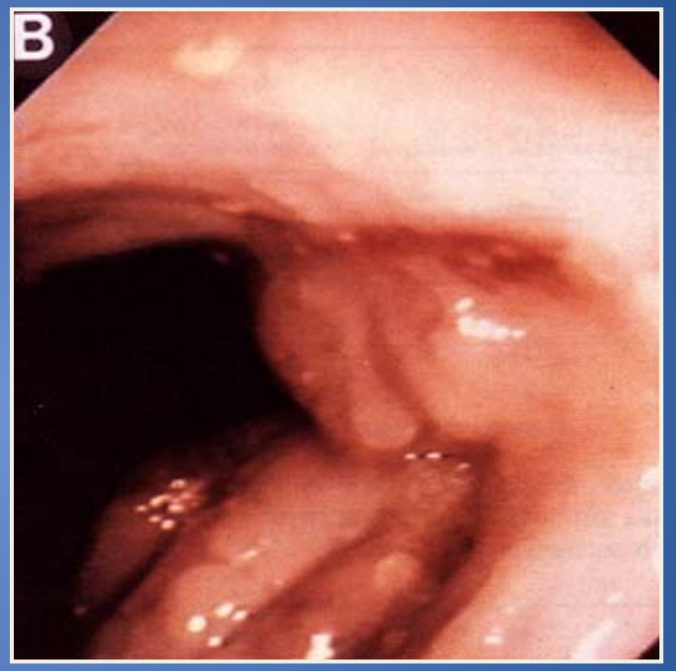
Anti-TNF: 50-65%%

Katz, *J Clin Gastroenterol* 2007

Biologic era in IBD management: Mucosal Healing



Pretreatment

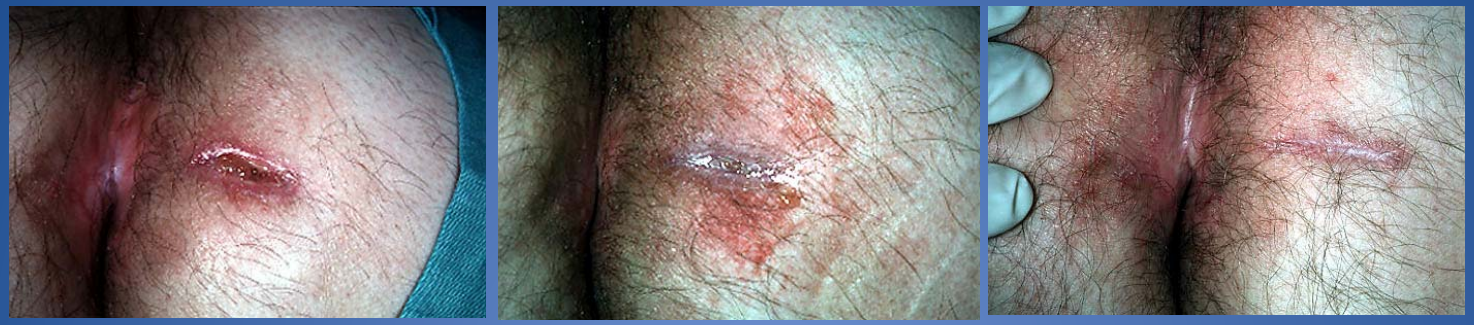


4 Weeks posttreatment

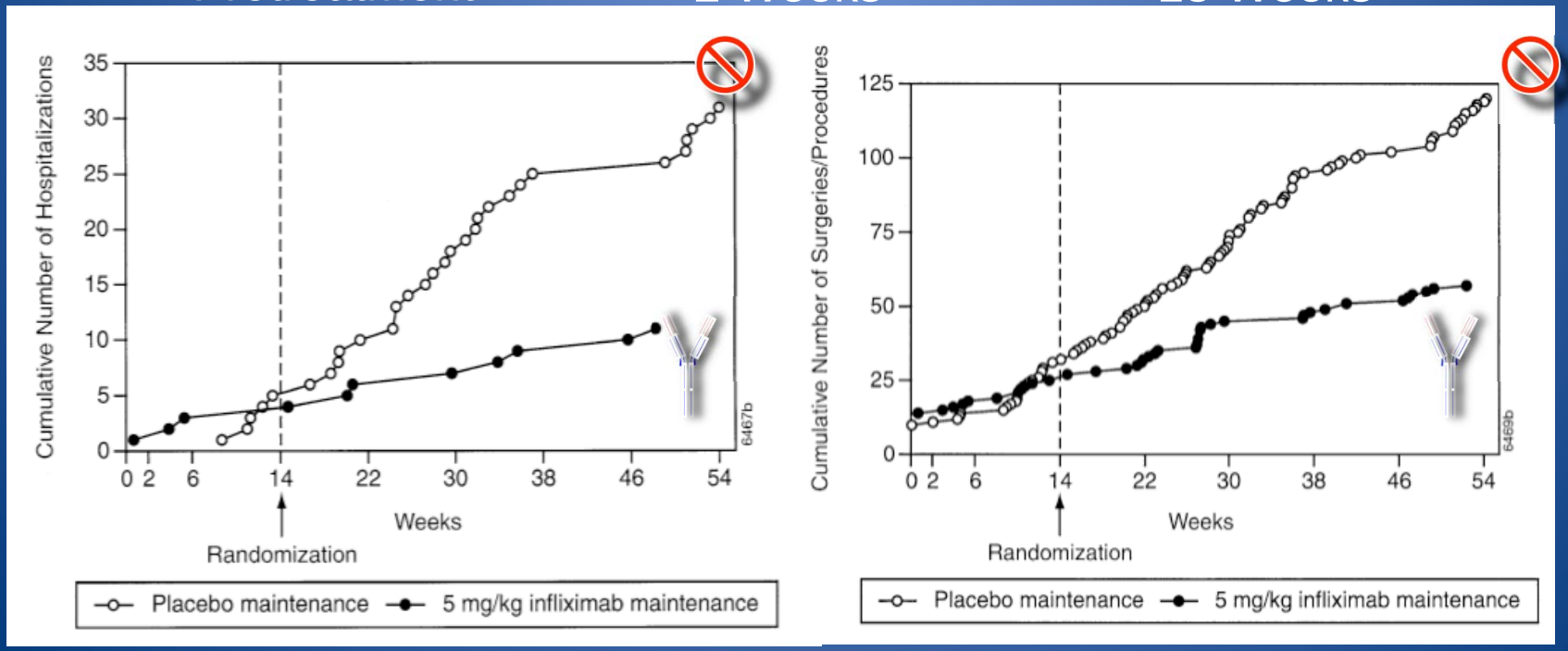
van Dullemen HM et al. *Gastroenterology.* 1995;109:129.

Present DH, et al. *N Engl J Med.* 1999;340:1398–1405.

Anti-TNF antibody infliximab revolutionized CD treatment



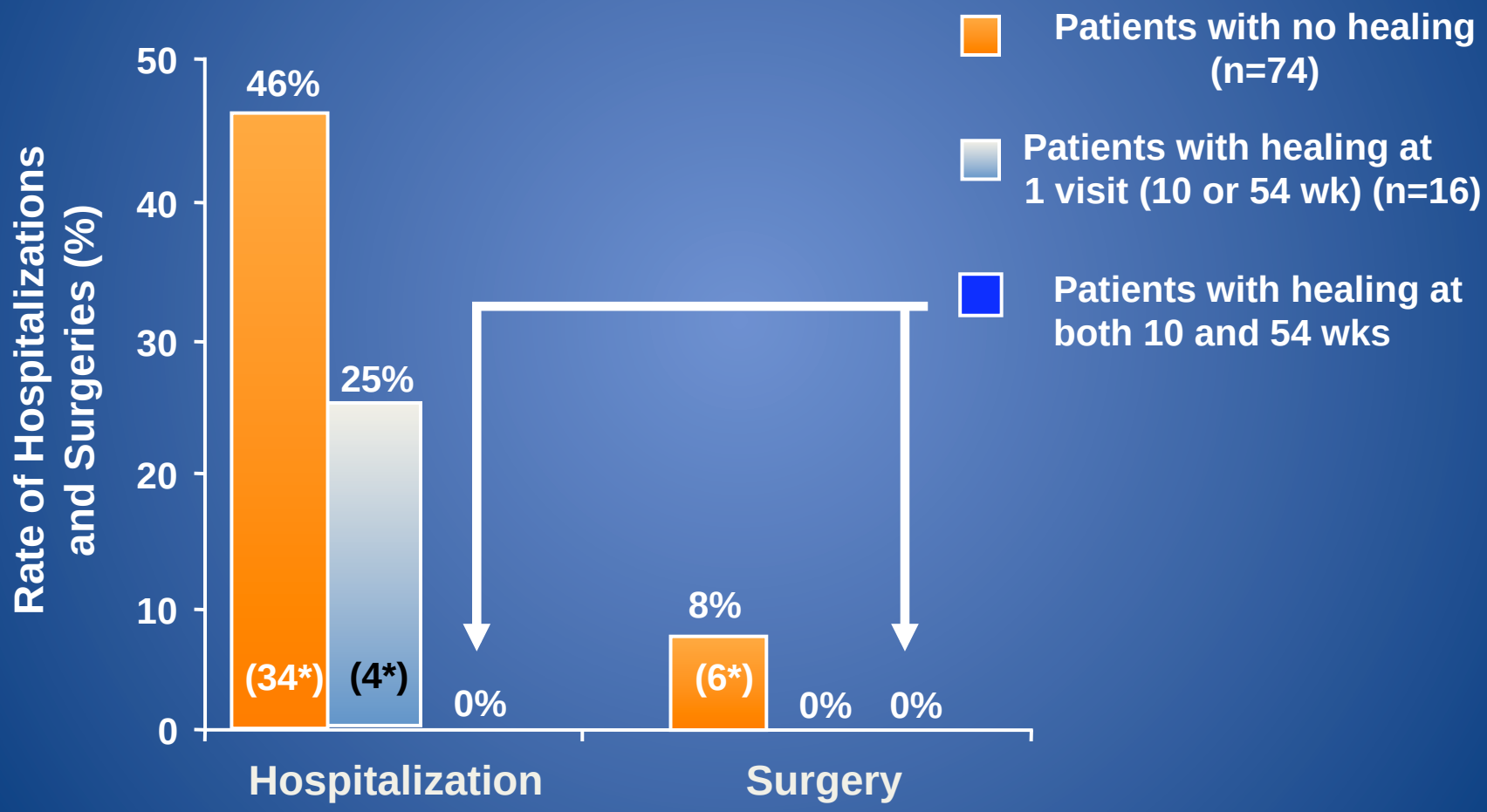
Pretreatment 2 Weeks 18 Weeks



NEJM 1999;340:1398; Gastro 2005; 128:862-869

Infliximab: ACCENT I

Endoscopic Healing and Reduced Hospitalizations and Surgeries: Infliximab maintenance for Crohn's disease



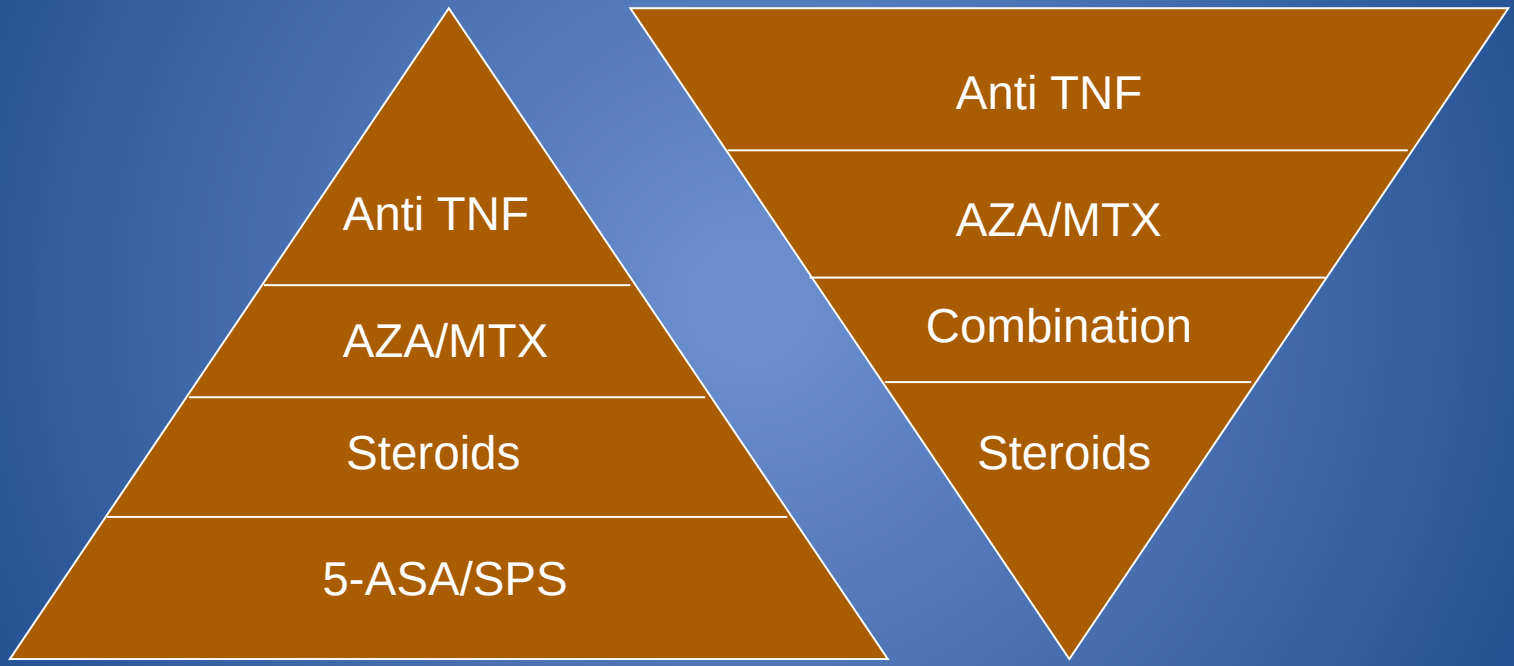
*Number per 100 patients

Rutgeerts P et al. *Gastroenterology.* 2002;123(suppl):43.M2138.

Need for New Therapies?

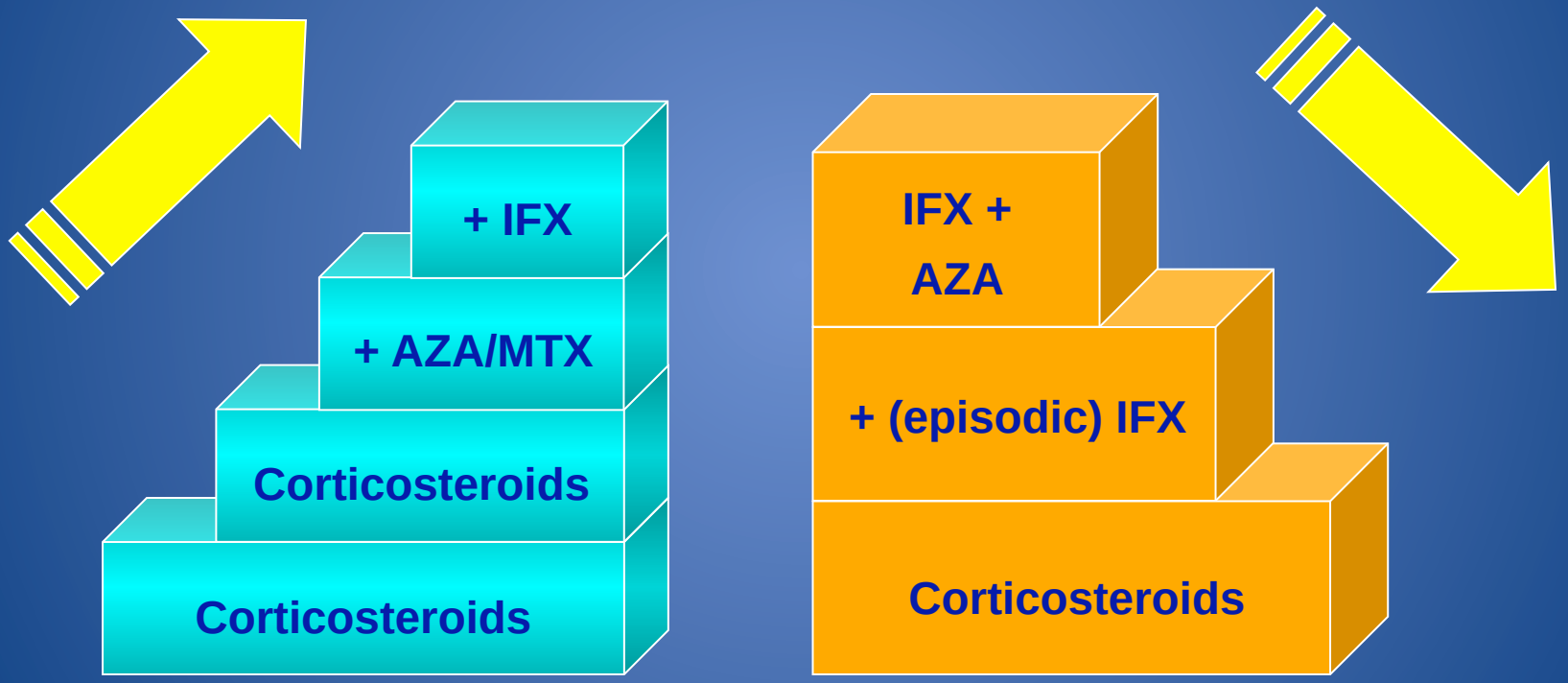
- Lack of sustained remission
  - Loss of response to Anti-TNF agents
- Need to change natural history of disease
  - Avoidance of surgery, complications
- **Solution?**
  - Change the treatment paradigm
  - Develop new drugs

Step-Up and Top-Down Therapy for Crohn's Disease



Lichtenstein GR et al. *Inflamm Bowel Dis*. 2004;10:S2–S10.

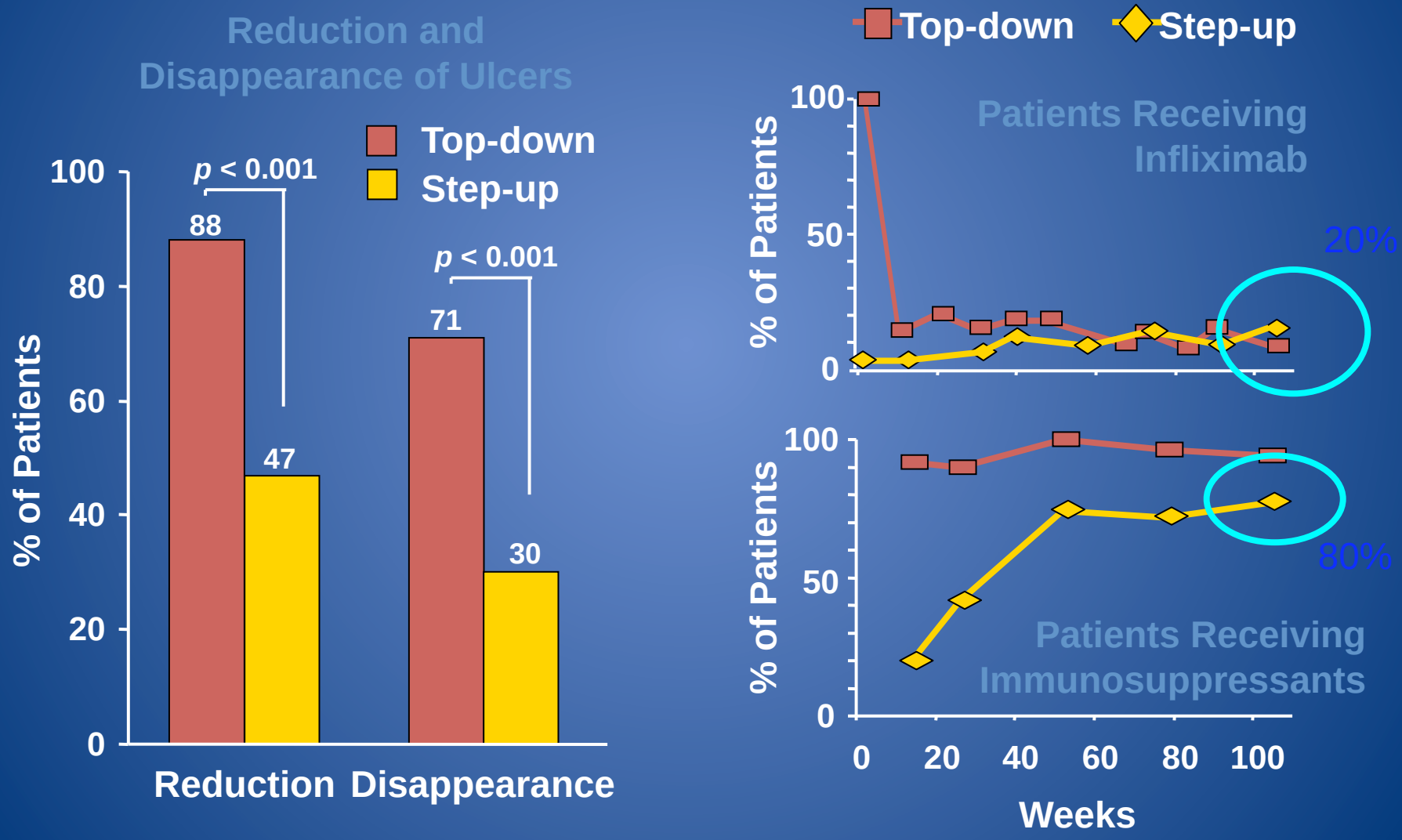
New Approaches to Therapeutic Intervention in Crohn's Disease?
The "Step-up" vs "Top-down" Trial



AZA, azathioprine; IFX, infliximab; MTX, methotrexate.

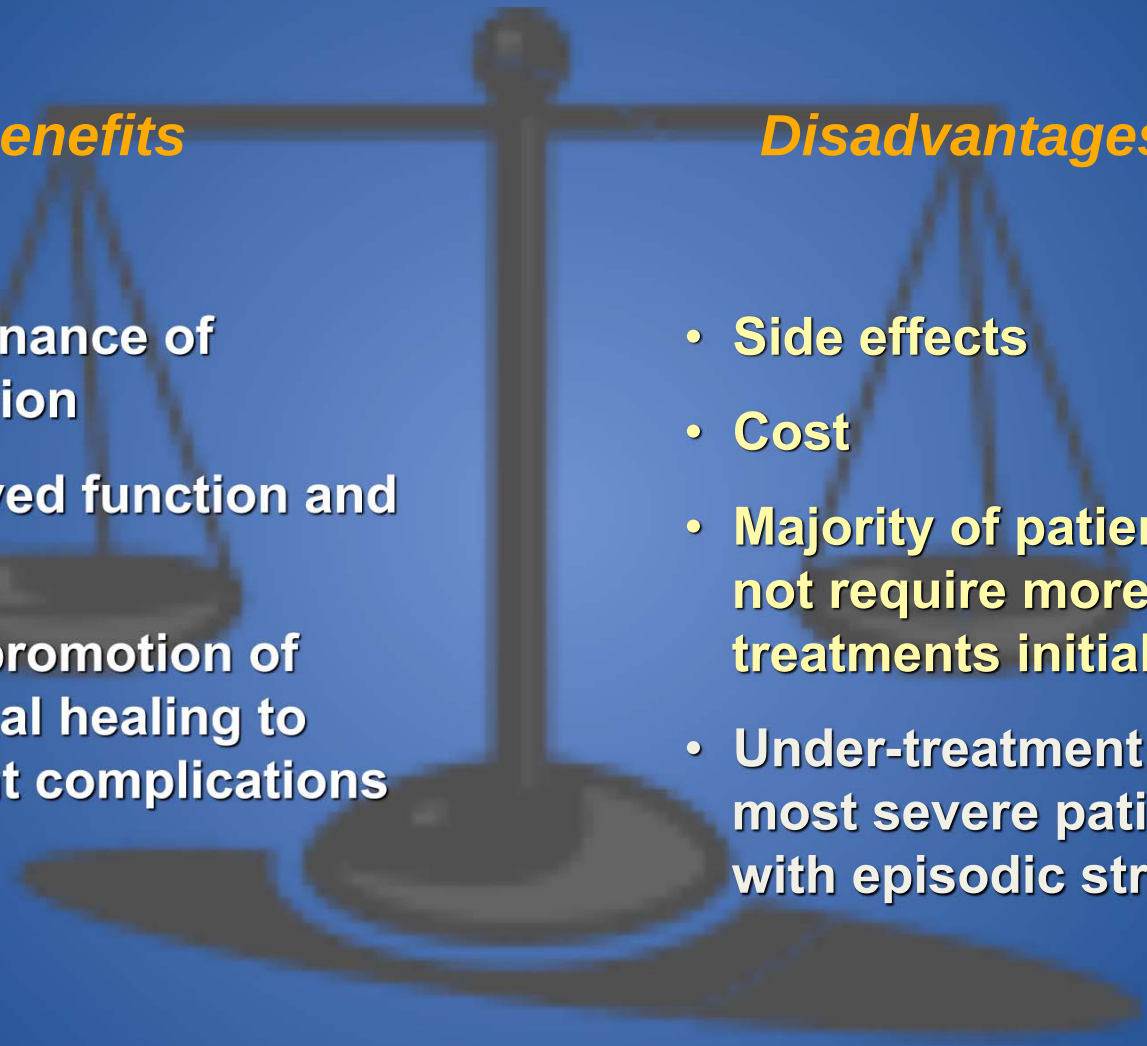
Top-Down Versus Step-Up Trial

Clinical Results at 2 Years



Hommes D, et al. DDW 2006, Abstract 749.; D'Haens GR, et al. DDW 2006. Abstract 764.

Weighing the Value of Top-Down Therapy



Benefits

- Maintenance of remission
- Improved function and QOL
- Early promotion of mucosal healing to prevent complications

Disadvantages

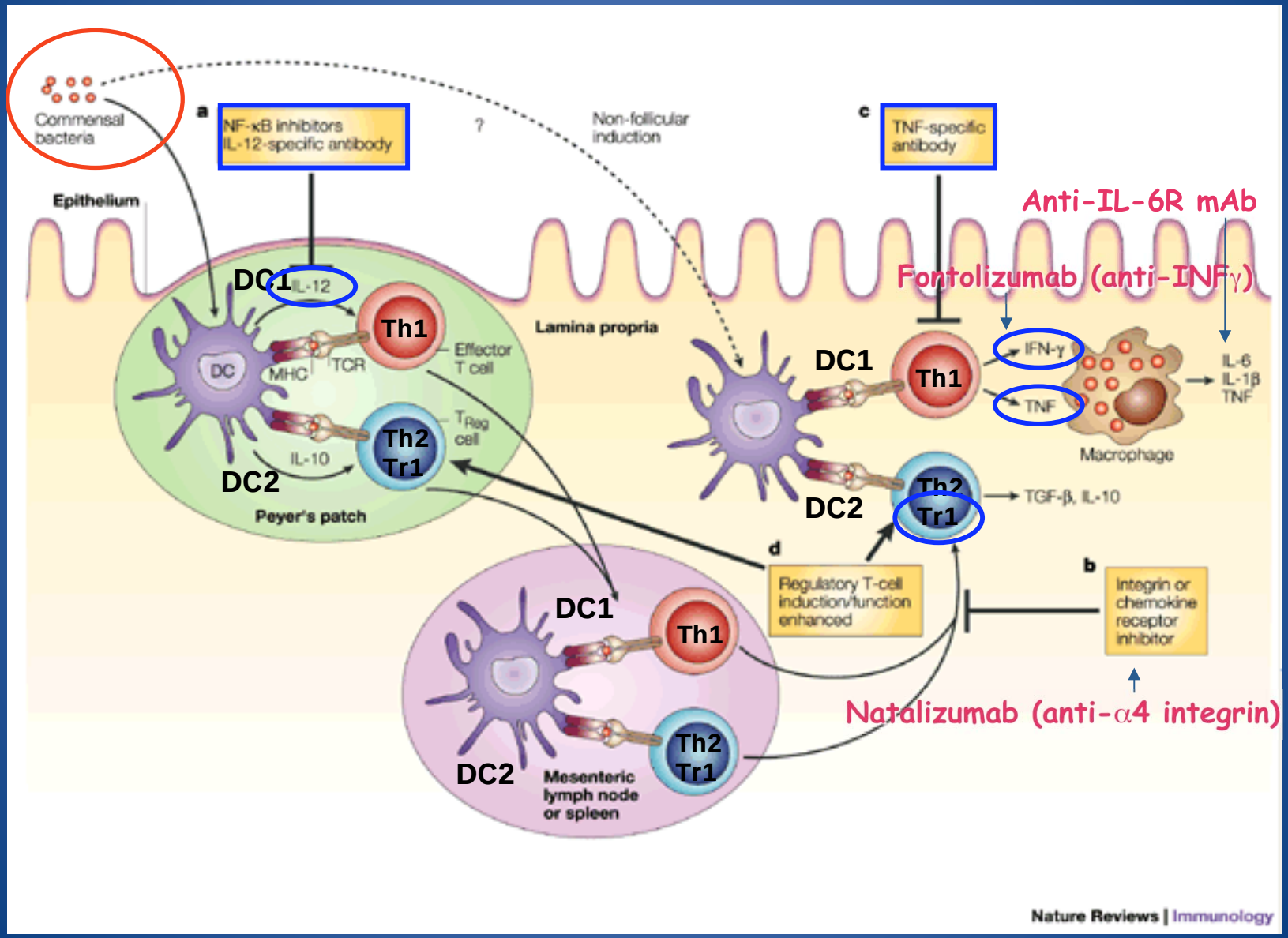
- Side effects
- Cost
- Majority of patients may not require more potent treatments initially
- Under-treatment of most severe patients with episodic strategy?

Lichtenstein GR, et al. *Inflamm Bowel Dis*. 2004;10:S2–S10.
Caprilli R, et al. *Digestive Liver Dis*. 2005;37:973–979.

Developing New Drugs for IBD

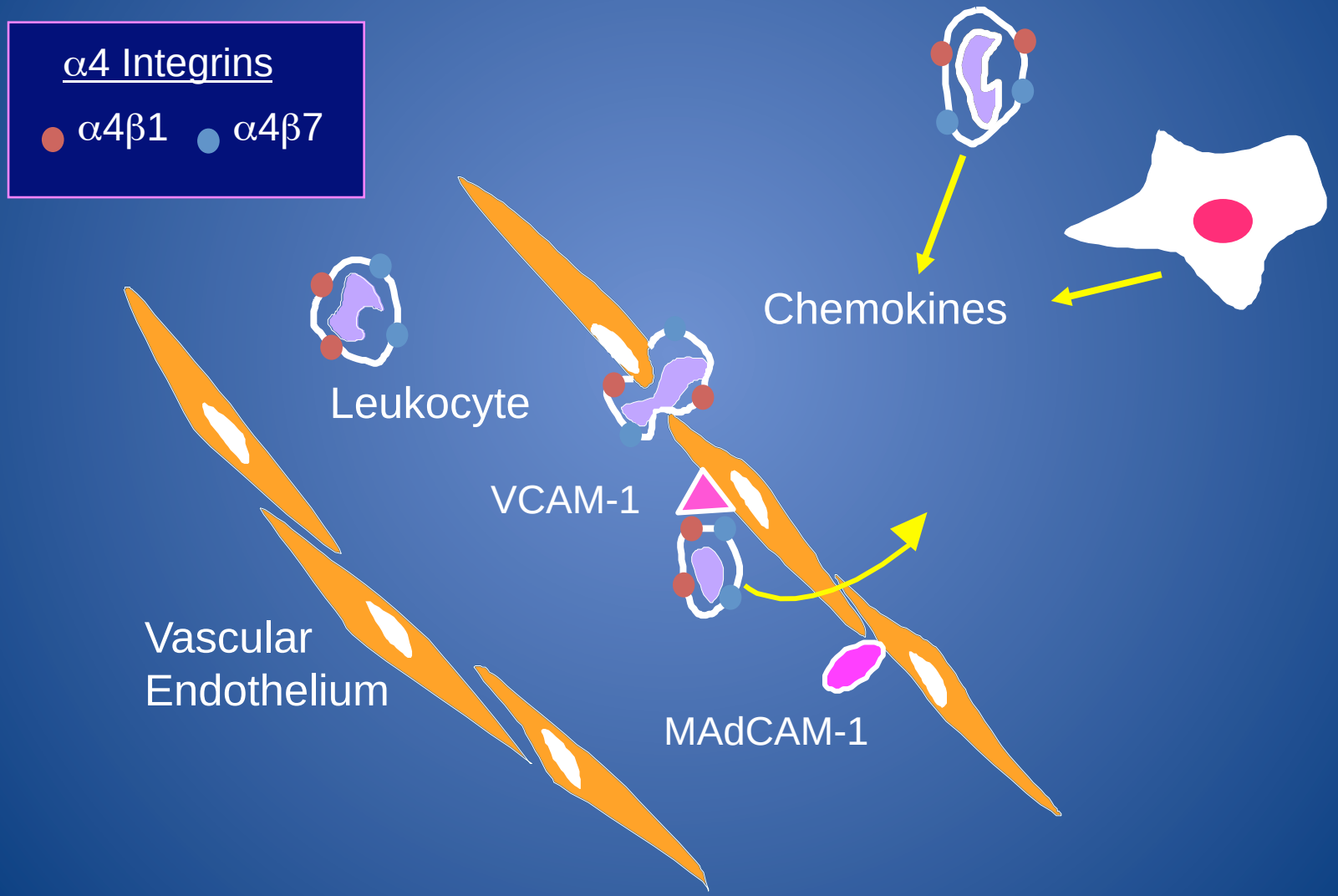
- Neutralize Major Effector Cytokine
- Enhance Counter-regulatory Response
- Enhance Regulatory Pathways (Cellular, Neurohumoral)
- Inhibit Amplification of Inflammation
- Manipulate Antigen Exposure (Enhance Barrier Function, Alter Microflora)

Targeting New Drugs in Crohn's Disease



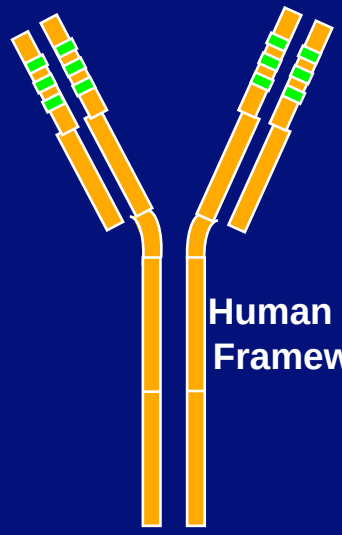
Adhesion and Recruitment

Mucosal and Inflammatory Zip Codes



Construct of Natalizumab

Complementarity-Determining Regions (CDRs)



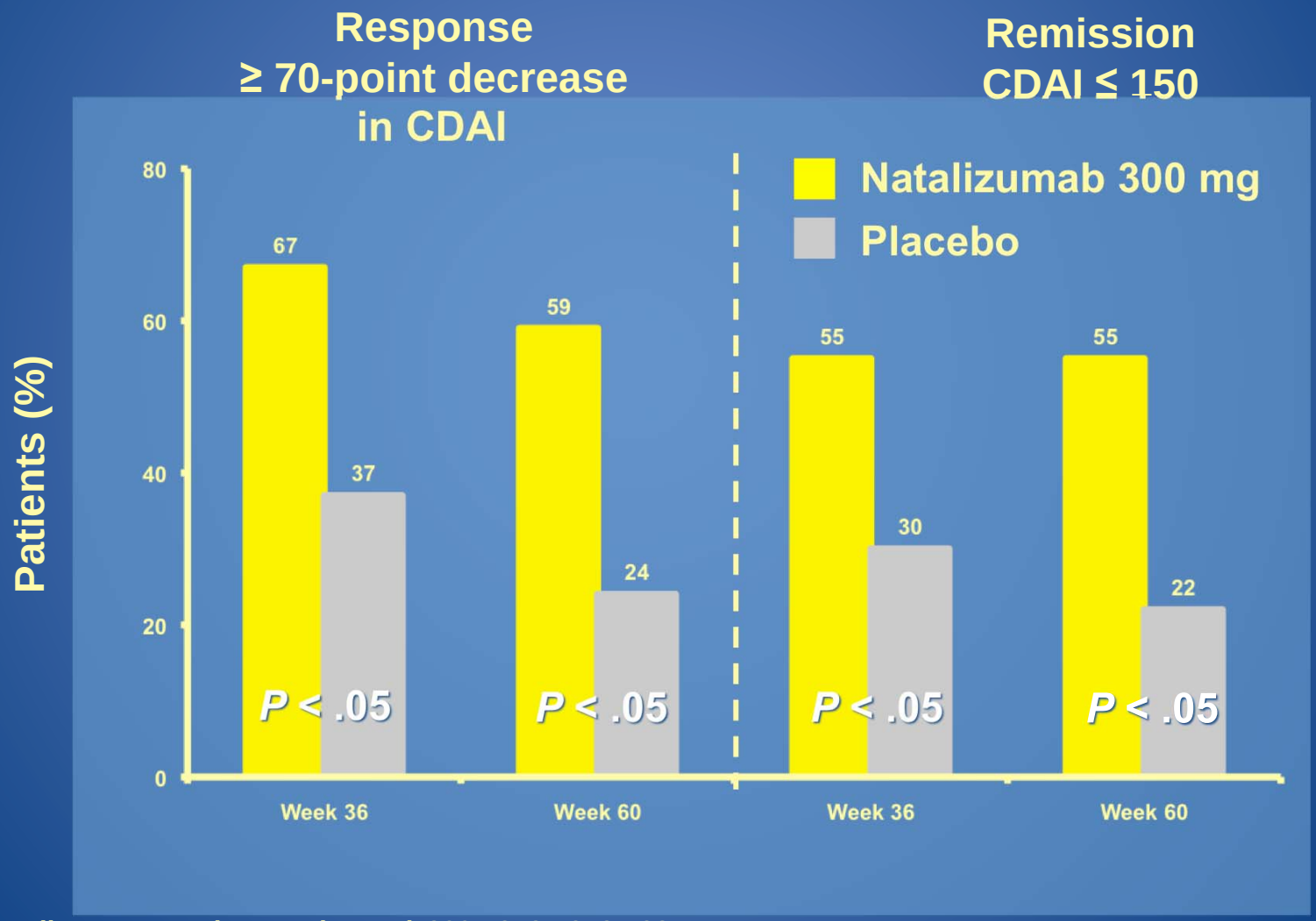
Human IgG_4 Framework

Natalizumab

Humanized mAb against α4-integrins

Human IgG_4 framework with CDRs grafted from murine antibodies

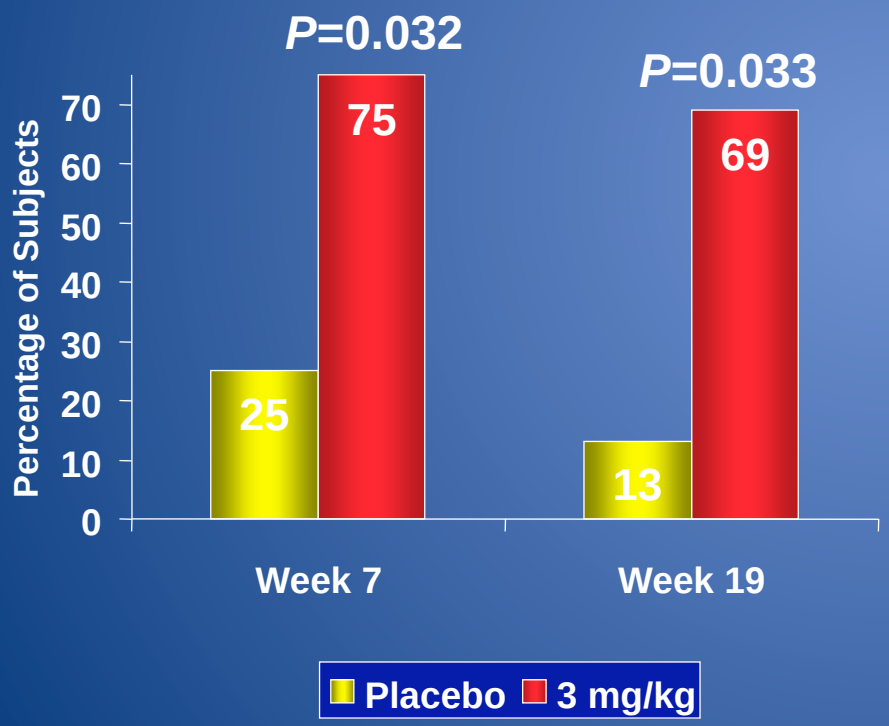
Natalizumab as Maintenance Therapy for Crohn's Disease: *ENACT-2 Trial*



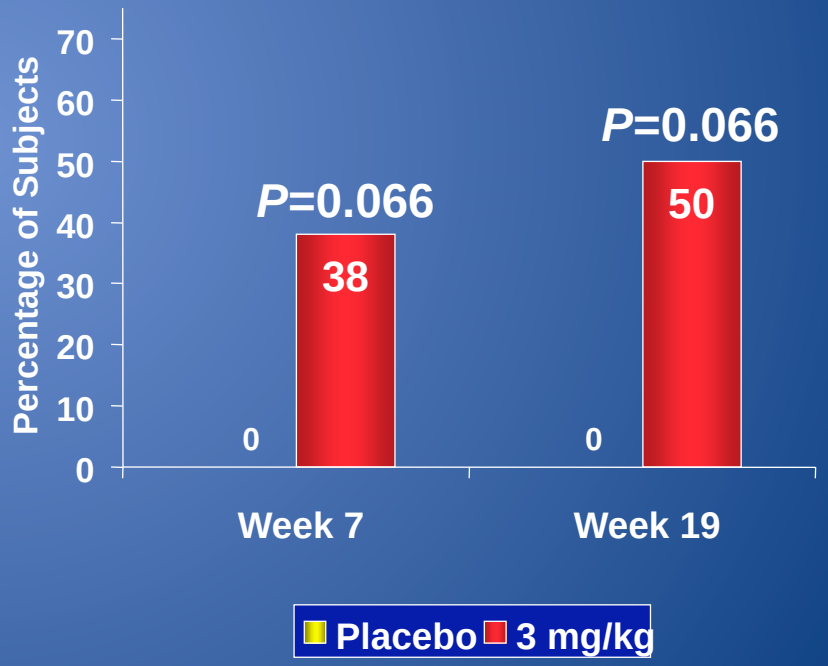
Sandborn WJ et al. *N Engl J Med.* 2005;353:1912-1925.

Anti-IL-12 (ABT-874) in Active Crohn's Disease

Patients With Clinical Response (Decrease in CDAI ≥100)



Patients With Clinical Remission (CDAI ≤150)



Mannon PJ et al. *N Engl J Med*. 2004;251:2069-2079.

The chronic inflammation of IBD is due to a dysregulated immune response to antigens in the intestine

- Innate and adaptive immune system
- Epithelial barrier function
- Composition of microbial flora
- Genetic and environmental exposures
- Defects in regulatory mechanisms